CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210498Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA (Original-1)
Application Number(s)	210498
Priority or Standard	Standard
Submit Date(s)	June 30, 2017
Received Date(s)	June 30, 2017
PDUFA Goal Date	June 30, 2018
Division/Office	DOP2/OHOP
Established Name	Binimetinib
(Proposed) Trade Name	MEKTOVI™
Pharmacologic Class	Kinase inhibitor
Code name	MEK-162, ARRY-162, ARRY-438162
Applicant	Array BioPharma Inc.
Formulation	15 mg tablets
Dosing Regimen	45 mg orally twice daily in combination with encorafenib
Applicant Proposed Indication/Population	In combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test
Recommendation on Regulatory Action	Regular approval
Recommended Indication/Population	In combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADaM	Analysis Data Model
ACAT™	Advanced Compartmental Absorption and Transit Model
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BIRC	blinded independent review committee
BLA	biologics license application
BORR	best objective response rate
BP	blood pressure
BPM	beats per minute
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
Cmax	maximum concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CORR	confirmed objective response rate
CP	cross point
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CuSCC	cutaneous squamous cell carcinoma
DCR	disease control rate
DDI	drug-drug Interaction
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DOR	duration of response
D-R	dose-response

ECG	electrocardiogram
ECHO	echocardiography
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
eCTD	electronic common technical document
EFT	embryo-fetal toxicity
EOT	end of therapy
E-R	exposure-response
FACT-M	Functional Assessment of Cancer Therapy - Melanoma
FAS	full analysis set
FDA	Food and Drug Administration
FPFV	first patient's first visit
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
HLGT	higher level group term
HLT	higher level term
HR	hazard ratio
IC_{50}	half maximal effective concentration
IEC	independent ethics committee
ILD	interstitial lung disease
IND	Investigational New Drug
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
KM	Kaplan-Meier
Km	substrate concentration at half the maximum velocity
Kps	drug tissue:plasma partition coefficients
LVEF	left ventricular ejection fraction
MAED	MedDRA-based Adverse Event Diagnostics
mDOR	mean duration of response
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
MMRM	mixed effect model for repeated measures
mOS	median overall survival
MTD	maximum tolerated dose
MUGA	multi-gated acquisition (scan)
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCT	ophthalmic coherence T
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate

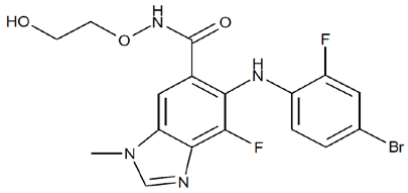
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiologically based pharmacokinetic
PD	progressive disease
PD	pharmacodynamics
PEAR	population estimates for age-related
PFS	progression free survival
PI	prescribing information
PK	pharmacokinetics
PMA	premarket approval
PMC	postmarketing commitment
PMR	postmarketing requirement
popPK	population PK
PP	per protocol
PPI	patient package insert
PPS	per protocol set
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	Preferred Term
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RPED	retinal pigment epithelium detachment
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SD	stable disease
SDTM	study data tabulation model
SMQ	Standardized MedDRA Query
SOC	system organ class
TEAE	treatment emergent adverse event
TGI	tumor growth inhibition
TK	toxicokinetics
Tmax	time drug is present at maximum concentration
TTD	time to 10% deterioration
TTR	time to objective response
ULN	upper limit of normal
VAI	voluntary action indicated

1 Executive Summary

1.1. Product Introduction

Proprietary Name:	MEKTOVI™
Established Name:	Binimetinib
Also Known As:	MEK-162, ARRY-162, ARRY-438162
Chemical Name:	5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide
Molecular Formula:	$C_{17}H_{15}BrF_2N_4O_3$
Molecular Weight:	441.23 g/mole
Dosage Forms:	Tablets, 15 mg
Therapeutic Class:	Antineoplastic
Chemical Class:	Small molecule
Pharmacologic Class:	MEK inbhitor
Mechanism of Action:	Inhibition of MEK1 and MEK2 enzyme by binimetinib prevents phosphorylation of ERK, leading to reduced cellular proliferation.

Chemical Structure:



Binimetinib (MEKTOVI™) is a new molecular entity. NDA 210498 was submitted for the proposed indication of treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation using a dose of 45 mg twice daily, in combination with encorafenib 450 mg daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of encorafenib and binimetinib under 21 CFR 314.105 for the indication, "Treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test," using a dose of encorafenib 450 mg daily and binimetinib 45 mg twice daily. The recommendation is based on the finding of increased progression-free survival (PFS) compared to vemurafenib in Study CMEK162B2301 (COLUMBUS, NCT01909453).

A more complete description of efficacy that includes overall survival, determination of an appropriate encorafenib dose for patients with concomitant use of a moderate CYP3A4 inhibitor, and dose adjustment guidelines for patients with comedications of CYP substrates whose PK may be affected by encorafenib remain to be determined in postmarketing studies.

COLUMBUS was an open-label, randomized, multicenter, two-part clinical trial of encorafenib in combination with binimetinib for adults with unresectable or metastatic melanoma harboring a V600E or V600K mutation. In Part 1, patients were randomized 1:1:1 to receive either encorafenib (450 mg daily) in combination with binimetinib (45 mg twice daily) ("Combo 450"), encorafenib alone (300 mg daily), or vemurafenib (960 mg twice daily). The Combo 450

regimen used in the pivotal study and proposed for marketing authorization were based on results from dose-finding Study CMEK162X2110, and was supported by dose-response and exposure-response analyses contained in this review. Higher doses of encorafenib resulted in dose limiting kidney toxicity.

The primary endpoint of COLUMBUS was PFS, determined based on tumor assessment (RECIST version 1.1 criteria) as per blinded independent central review (BIRC). The Combo 450 arm had significantly longer PFS compared to the vemurafenib arm, with a stratified log-rank test p-value of <0.0001. The estimated median PFS times were 14.9 months (95% CI: [11.0, 18.5]) for the Combo 450 arm and 7.3 (95% CI: [5.6, 8.2]) for the vemurafenib arm. The stratified hazard ratio of PFS for the Combo 450 arm compared to the vemurafenib arm was 0.54 (95% CI: [0.41, 0.71]).

A key secondary endpoint of COLUMBUS, intended by the applicant to assess the contribution of binimetinib to the efficacy of the combination, was PFS in the Combo 450 arm versus the encorafenib monotherapy arm. The Combo 450 arm did not demonstrate a significant improvement in PFS when compared to the encorafenib arm, with a two-sided stratified log-rank test p-value of 0.0513. The estimated median PFS times were 14.9 months (95% CI: [11.0, 18.5]) for the Combo 450 arm and 9.6 (95% CI: [8.7, 14.8]) for the encorafenib arm. The stratified hazard ratio of PFS for the Combo 450 arm compared to the encorafenib arm was 0.75 (95% CI: [0.56, 1.00]).

However, in presubmission meetings and correspondence with the applicant, FDA noted that the trial design for Part 1 of COLUMBUS, which employs a higher dose of encorafenib in the combination arm than in the single-agent arm, would not allow an adequate assessment of the contribution of binimetinib treatment effect in the combination. The applicant responded that the dose of encorafenib as monotherapy could not be increased for reasons of unacceptable toxicity, as the addition of binimetinib mitigates some of the encorafenib-associated toxicities. Part 2 was thus added to the study to respond to the FDA's concern. In Part 2, patients were randomized 3:1 to receive either encorafenib (300 mg daily) in combination with binimetinib (45 mg twice daily) ("Combo 300") or encorafenib alone (300 mg daily).

The Combo 300 arm exhibited a numerical improvement in progression-free survival when compared to encorafenib monotherapy, though no formal test was performed due to hierarchical testing rules. The estimated median PFS times were 12.9 months (95% CI: [10.1, 14.0]) for the Combo 300 arm and 9.2 (95% CI: [7.4, 11.0]) in the encorafenib group. The stratified hazard ratio of PFS for the Combo 300 arm compared to the encorafenib group was 0.77 (95% CI: [0.61, 0.97]).

The review team concluded that the clinically and statistically significant PFS advantage seen with encorafenib and binimetinib compared to vemurafenib constitutes substantial evidence of effectiveness, and that, based on the totality of the data generated by COLUMBUS, both encorafenib and binimetinib are required to yield the observed efficacy.

1.3. Benefit-Risk Assessment

The applicant has proposed that encorafenib (BRAFTOVI™), a RAF inhibitor, in combination with binimetinib (MEKTOVI™), a MEK inhibitor, be approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation based on a prolongation of progression-free survival compared to a standard of care agent (vemurafenib). The review team recommends regular approval of encorafenib and binimetinib for the proposed indication, at the proposed doses of 450 mg daily and 45 mg twice daily, respectively.

Patients with untreated unresectable or metastatic melanoma have a dismal prognosis, with a 5-year overall survival of <10%. BRAF mutations are associated with several high risk features of melanoma including truncal primary, earlier age of onset, lack of chronic skin damage, and shortened survival. Since 2011, the FDA has approved 7 new therapies for unresectable or metastatic melanoma. Standard of care treatment options now include immunotherapeutic agents (ipilimumab, nivolumab, pembrolizumab) given alone or in combination, which prolong median survival but are associated with immune-related adverse reactions that can be life-threatening or fatal, or, for patients with BRAF V600 mutations, RAF and MEK inhibitor combinations (vemurafenib with cobimetinib and dabrafenib with trametinib), which also prolong median survival but are associated with serious toxicities including secondary skin malignancies, cardiac failure, and ocular toxicities. None of these agents are curative, and thus an unmet medical need persists.

In the COLUMBUS study, patients treated with encorafenib in combination with binimetinib had a median progression-free survival of 14.9 months, compared to 7.3 months in patients treated with vemurafenib (hazard ratio 0.54 (95% CI: [0.41, 0.71]), p-value <0.0001). Patients treated with encorafenib in combination with binimetinib also had a trend toward improved overall survival compared to patients treated with vemurafenib, but survival data is not yet mature, and statistical testing will not be performed on this endpoint. While limitations in study design prevented a statistically robust demonstration of the contribution of each individual drug to the overall treatment effect, the totality of the data generated on COLUMBUS, which incorporated an encorafenib monotherapy arm, supported the FDA's conclusion that both drugs are required to maximize clinical benefit. There is no identified advantage for encorafenib and binimetinib over other available RAF and MEK inhibitor combinations, but it is acknowledged that modest differences in side effect profiles may provide options for individualized treatment selection for specific patients.

Important toxicities observed on clinical trials of encorafenib and binimetinib include new primary malignancies, tumor promotion in BRAF wild-type tumors, ocular toxicities (serious retinopathy, retinal vein occlusion, and uveitis), hemorrhage, QT prolongation, cardiomyopathy, venous thromboembolism, interstitial lung disease, hepatotoxicity, and rhabdomyolysis. However, these toxicities were generally manageable with dose interruption or reduction, and only 9% of subjects on COLUMBUS terminated therapy due to

an adverse reaction. These results provide substantial evidence that the combination of encorafenib and binimetinib is tolerable for most patients.

Given the tolerability of encorafenib in combination with binimetinib, the clinical benefit of the combination appears to outweigh the risks for patients with unresectable or metastatic melanoma harboring a BRAF V600 mutation.

	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients with unresectable or metastatic melanoma have a 5-year overall survival of <10%. • Patients whose disease harbors a BRAF V600 mutation have a worse prognosis.	Unresectable or metastatic melanoma is a fatal disease.
Current Treatment Options	• FDA-approved therapies for unresectable or metastatic melanoma include immunotherapy agents (ipilimumab, nivolumab, pembrolizumab), BRAF inhibitors (vemurafenib, dabrafenib), and MEK inhibitors (cobimetinib, trametinib). • PD-1 inhibitors prolong median survival, but are associated with immune-related adverse reactions which can be life-threatening. • BRAF and MEK inhibitors prolong median survival in patients with BRAF V600 mutations, but serious toxicities, including secondary skin cancers, left ventricular dysfunction, and ocular toxicities can occur.	There is a need for additional effective therapies for the treatment of unresectable or metastatic melanoma. Differences in activity and side effect profiles among therapies approved for this disease provide options for individualization of therapy.
Benefit	• In COLUMBUS, patients treated with encorafenib in combination with binimetinib had a median progression-free survival of 14.9 months, compared to 7.3 months in patients treated with vemurafenib. • In COLUMBUS, patients treated with encorafenib in combination with binimetinib had a trend toward improved overall survival compared to patients treated with vemurafenib, but survival data is not yet mature, and statistical testing will not be performed on this endpoint.	There is substantial evidence of effectiveness for encorafenib and binimetinib in the treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. A more complete description of survival needs to be determined.

	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most common adverse reactions (≥25%) included fatigue, nausea, vomiting, abdominal pain, and arthralgia. • Important toxicities of encorafenib include new primary malignancies, tumor promotion in BRAF wild-type tumors, hemorrhage, uveitis, and QT prolongation. • Important toxicities of binimetinib include cardiomyopathy, venous thromboembolism, ocular toxicities (serious retinopathy, retinal vein occlusion, and uveitis), interstitial lung disease, hepatotoxicity, rhabdomyolysis, and hemorrhage. • Nonclinical data suggest that encorafenib and binimetinib may cause embryo-fetal toxicity (EFT). • An appropriate dose for patients with concomitant use of a moderate CYP3A4 inhibitor has not been established. • Dose adjustment guidelines for patients who require concomitant use of CYP3 substrates have not been established.	The overall safety profile of encorafenib and binimetinib is acceptable for patients with unresectable or metastatic melanoma. Dose adjustment guidelines for certain drug-drug interactions need to be clarified.
Risk Management	• The protocol included monitoring for risks and instructions for intervention. With this in place, serious toxicities could be mitigated by dose interruption or reduction. • The proposed labeling includes warnings, dose modifications and management guidelines for serious toxicities.	A patient medication guide is recommended for encorafenib and a patient package insert is recommended for binimetinib to inform and educate patients of the risks and when to seek medical attention. Labeling should include warnings for important toxicities, and instructions for monitoring and dose modifications for toxicities.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:	Section where discussed
	□ Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	Section 8.1.3
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

Ashley Ward, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Amecian Cancer Society reports there will be approximately 91,270 new cases of melanoma in 2018, with approximately 9,320 people expected to die of the disease. Approximately 84% of cases will be localized or confined to the primary site, 9% will have spread to regional lymph nodes, and 4% will have metastasized to distant sites. Melanoma is more frequent in men (60% of cases) than women (40% of cases). Median age at diagnosis is 64 years, with approximately 70% of cases ocurring in patients ≥ 55 years of age. The incidence of melanoma of the skin by race reported in the SEER data for 2014 (cases per 100,000 people) is: White: 31.4, Black: 1.0, Asian/Pacific Islander:1.6, American Indian/Alaska Native: 3.1, and Hispanic: 5.4. The 5-year overall survival for all-comers with melanoma is 92%; however, once melanoma is metastatic to distant sites, the 5-year overall survival is less than 10%.

Approximately 40-60% of melanomas contain a mutation in the BRAF gene that leads to constitutive activation of downstream signalling in the MAP kinase pathway. In 80-90% of these cases, the activating mutation consists of the substitution of glutamic acid for valine at amino acid 600 (V600E). BRAF mutations are associated with several high risk features of melanoma including truncal primary, earlier age of onset, lack of chronic skin damage, and shortened survival. The most important prognostic factors in metastatic melanoma are site(s) of metastases and the presence of elevated serum lactate dehydrogenase (LDH). Prognosis is particularly poor in patients with the American Joint Committee on Cancer (AJCC) stage IV M1c melanoma in which the tumor has metastasized to visceral organs (other than the lung) or when there are any distant metastases accompanied by elevated LDH.

2.2. Analysis of Current Treatment Options

Table 1: Available FDA-Approved Therapies Indicated for the Treatment of Patients with Unresectable or Metastatic Melanoma

summarizes FDA approved therapies for use in advanced or metastastic melanoma. Current standard of care consists of either a CTLA-4 inhibitor (ipilimumab), a PD-1 inhibitor (pembrolizumab or nivolumab) or, for patients whose disease harbors a BRAF V600 mutation, a BRAF inhibitor, typically in combination with a MEK inhibitor. Ipilimumab and pembrolizumab are approved for patients regardless of BRAF mutation status, while nivolumab has regular approval for BRAF wild-type patients and accelerated approval for patients with BRAF V600 mutations. PD-1 inhibitors are associated with relatively modest response rates (33-34%, mostly partial responses), but responding patients do well, with survival curves having a long "tail." However, ipilimumab and the PD-1 inhibitors are associated with immune-related adverse reactions, which can be life-threatening or fatal (see Table 1). BRAF and MEK inhibitors are typically associated with higher response rates (66-70%, mostly partial responses), but relapse due to acquired resistance mutations is inevitable, and these agents are associated with other important toxicities, including skin neoplasia, left ventricular dysfunction, and ocular toxicities. There are no curative therapies for patients with advanced or metastatic melanoma.

Table 1: Available FDA-Approved Therapies Indicated for the Treatment of Patients with Unresectable or Metastatic Melanoma

Drug	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect	Notable Toxicities
Chemotherapy[1]					
DTIC (dacarbazine)[2]	1975	Single-Arm	ORR	ORR 5-20%	• Leukopenia, thrombocytopenia, anemia • Anorexia, nausea, vomiting, fever, myalgias, malaise • Hepatic vein thrombosis, hepatocellular necrosis
General Immune Therapy					
Proleukin (aldesleukin)[2]	1998	Multicenter Single Arm	ORR	ORR 16% (CR 6%); DOR CR: 59+ m (3 to 122+ m) CR or PR: 59+ m (1 to 22+m)	• Fever, hypotension, chills, dyspnea, rash, malaise, confusion • Nausea, vomiting, diarrhea, acute kidney failure • Ventricular tachycardia, myocardial infarction • Immune-related organ inflammation
Checkpoint Inhibitor					
Yervoy (Ipilimumab)[2]	2011	Multicenter, randomized, blinded, active-controlled three-arm	OS ORR	**Ipilimumab vs. gp100**: OS: HR 0.66 (95% CI: 0.51, 0.87) median 10 vs. 6 m BORR: 10.9% vs. 1.5% mDOR: not reached in either arm	• Severe/fatal immune-mediated adverse events (including hepatitis, endocrinopathies, pneumonititis, nephritis and renal dysfunction, encelphalitis, and infusion reactions)
Keytruda (pembrolizumab)	2014	Multicenter, randomized, blinded, active-controlled three-arm	ORR PFS OS	**Pembrolizumab vs. Ipilimumab:** OS: HR 0.69 (95% CI: 0.52, 0.90) Median OS not reached mPFS: 4.1m vs 2.8m HR 0.58 (95% CI: 0.47, 0.72) ORR: 33% vs 12% CR: 6% vs 1%, PR: 27% vs 10%	• Severe/fatal immune-mediated adverse events (including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal failure, skin reactions including SJS and TEN, infusion-related reactions, organ transplant rejection, and complications of allogeneic stem cell transplant)
Opdivo (nivolumab)	2014	Multicenter, randomized, blinded, active-controlled three-arm	ORR PFS OS	**Nivolumab vs. Dacarbazine:** OS: HR 0.42 (95% CI: 0.30, 0.60) Median OS not reached mPFS: 5.1m vs 2.2m HR 0.43 (95% CI: 0.34, 0.56) ORR: 34% vs 9% CR: 4% vs 1%, PR: 30% vs 8%	• Severe/fatal immune-mediated adverse events (including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin reactions, encephalitis, infusion-related reactions, and complications of allogeneic stem cell transplant)

Drug	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect	Notable Toxicities
Opdivo and Yervoy (nivolumab and ipilimumab)	2015 [3]	Randomized, double-blind, active controlled, three-arm study	PFS OS ORR	**Nivolumab+Ipilimumab vs. Ipilimumab** mPFS: 11.5 vs. 2.9 m HR: 0.42 (95% CI: 0.34, 0.51) mOS: NR vs. 17.7m cORR: 50% (95% CI: 44, 45) vs 14% (95% CI: 10, 18) CR: 8.9% vs 1.9%, PR: 41% vs 12% mDOR: NR (range 1.2+, 15.8+m)	• Immune-mediated adverse events occurring at increased severity and frequency compared to either agent alone
BRAF/MEK inhibitors					
Zelboraf (vemurafenib) [5]	2011	Randomized, open-label, active controlled, two arm	OS PFS ORR	**Vemurafenib vs. DTIC** mOS: NR vs. 7.9 m HR: 0.44 (95% CI: 0.33, 0.59) mPFS: 5.3 vs. 1.6 m HR: 0.26 (95% CI: 0.20, 0.33) cORR: 48% (95% CI: 42, 55) vs 6% (95% CI: 3, 9) CR: 0.9% vs 0%, PR: 48% vs 6%	• Cutaneous and non-cutaneous malignancies (squamous cell carcinomas, keratoacanthomas) • Ocular toxicity (retinal vein occlusion, iritis, uveitis) • Hypersensitivity reactions and serious skin toxicity (SJS, TEN) • Hepatotoxitiy, renal failure, QT prolongation • Radiation sensitivity and recall, photosensitivity • Dupuytren's contracture and plantar fascial fibromatosis
Tafinlar (dabrafenib) [5]	2013	Randomized, open label, active controlled, two arm	PFS ORR	**Dabrafenib vs. Dacarbazine** mPFS: 5.1 vs. 2.7 m HR: 0.33 (95% CI: 0.20, 0.54) cORR: 52% (95% CI: 44, 59) vs 17% (95% CI: 9, 29) CR: 3% vs 0%, PR: 48% vs 17%	• Cutaneous and non-cutaneous malignancies (squamous cell carcinomas, keratoacanthomas) • Cardiomyopathy, uveitis, serious febrile reactions • Hypersensitivity reactions and serious skin toxicity (SJS, TEN) • Hemorrhage, hemolytic anemia, hyperglycemia
Mekinist (trametinib) [6] ≤ 1 prior therapy; no prior BRAF or MEK inhibitor	2013	Randomized, open-label, active-controlled, two arm	PFS ORR	**Trametinib vs. Chemotherapy** mPFS: 4.8 vs. 1.5 m HR: 0.47 (95% CI: 0.34, 0.65) cORR: 22% (95% CI: 17, 28) vs 8% (95% CI: 4, 15) CR: 2% vs 0%, PR: 20% vs 9%	• Cutaneous and non-cutaneous malignancies (squamous cell carcinomas, keratoacanthomas) • Hemorrhage, colitis, GI perforation, venous thromboembolism, cardiomyopathy • Ocular toxicities (uveitis, retinal vein occlusion) • Interstitial lung disease, serious febrile reactions, serious skin toxicity (SJS, TEN), hyperglycemia

Drug	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect	Notable Toxicities
Tafinlar and Mekinist (dabrafenib and trametinib) [6]	2014	Randomized, open-label, active-controlled, two arm portion of dose-escalation study	ORR PFS OS	**Dabrafenib+Trametinib vs.Dabrafenib** ORR 66% vs. 51% mDOR 9.2m vs. 10.2m mPFS: 9.3m vs. 8.8m HR: 0.75 (95% CI: 0.57, 0.99) mOS: 25.1m vs. 18.7m HR: 0.71 (95% CI: 0.55, 0.92)	• See toxicities associated with individual agents. • Pyrexia, hemorrhagic events and thromboembolic events occurred at a higher incidence and cutaneous malignancies at a lower incidence with the combination compared to single-agent dabrafenib
Cotellic and Zelboraf (cobimetinib and vemurafenib) [6]	2015	Randomized, double-blind, active controlled, two-arm study	PFS OS ORR	**Cobimetinib+Vemurafenib vs. Vemurafenib** mPFS: 12.3 vs. 7.2 m HR: 0.56 (95% CI: 0.45, 0.70) mOS: NR vs. 17 m cORR: 70% (95% CI: 64, 75) vs 50% (95% CI: 44, 56) CR: 16% vs 10%, PR: 54% vs 40% mDOR: 13 vs. 9.2 m	• See toxicities associated with vemurafenib • Also hemorrhage, cardiomyopathy, rhabdomyolysis • Alopecia, hyperkeratosis and erythema occurred at a lower incidence with the combination compared to single-agent vemurafenib

Source: Cotellic USPI; Dacarbazine USPI; Keytruda USPI; Mekinist USPI; Opdivo USPI; Proleukin USPI; Tafinlar USPI; Yervoy USPI; Zelboraf USPI
Abbreviations in Table: m, months; BORR, best objective response rate; CR, complete response; cORR, confirmed objective response rate; DOR, duration of response; HR, hazard ratio; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; +, response is ongoing.
[1] Hydroxyurea is also FDA-approved for treatment of melanoma but is of historical interest only and not clinically used for this indication.
[2] BRAF V600 mutation status unknown.
[3] Accelerated approval as per 21 CFR 601, subpart E.
[4] Accelerated approval as per 21 CFR 314.510 of subpart H.
[5] Patient selection based on BRAF V600E mutation-positive tumors.
[6] Patient selection based on BRAF V600E or V600K mutation-positive tumors.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Encorafenib and binimetinib are new molecular entities (NME) and neither is currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

On January 24, 2012, Novartis submitted an IND for the development of binimetinib with encorafenib for treatment of patients with unresectable or metastatic melanoma harboring BRAF V600 mutations. IND 113850 opened in DOP2, and the two trials contributing to the efficacy analysis portion of this application, (CMEK162B2301 and CMEK162X2110), were eventually conducted under this IND.

On April 29, 2013, a Type B, End of Phase 2 (EOP2) meeting was held to discuss Novartis' proposed trial, Study CMEK162B2301, entitled, "A Phase III randomized, 3-arm, partially blinded, placebo controlled, multicenter, study of the Combination of LGX818 plus MEK162 compared with vemurafenib, and of LGX818 compared with vemurafenib for the treatment of patients with unresectable stage IIIB, IIIC or Stage IV melanoma with BRAF V600 mutation." Key agreements and comments:

- FDA agreed progression-free survival (PFS) was an acceptable primary endpoint for the proposed trial and may support a request for regular approval provided a statistically significant, robust and clinically meaningful effect on PFS that is large in magnitude is observed.
- FDA noted that a companion diagnostic test would be required for approval of encorafenib and recommended that Novartis stratify patients based on BRAF V600 mutation type (i.e., V600E vs. V600K).
- FDA did not object to the proposed statistical analysis methods for independent comparisons of both the LGX818/MEK162 combination versus vemurafenib and LGX818 versus vemurafenib. FDA noted that the Bayesian analysis for estimating the contribution of MEK162 to the combination of LGX818 plus MEK162 would be considered exploratory.
- FDA recommended that the primary analyses of PFS and OS be conducted at a prespecified number of events, that the O'Brien-Fleming method be used for alpha adjustment for interim analysis of overall survival (OS), and that given the proposal to ignore or group strata, the primary analysis should be unstratified.
- FDA strongly recommended that Novartis submit a Pre-Submission to CDRH to discuss the analytical validation necessary to support premarket approval (PMA) for the companion diagnostic test.

On June 14, 2013, a new clinical protocol for Study CMEK162B2301 was submitted to IND 113850. CMEK162B2301 was proposed as a prospective, randomized (1:1:1) open-label, multi-center study comparing LGX818 in combination with MEK162 (450 mg once daily and 45 mg twice daily, respectively) to LGX818 monotherapy (300 mg once daily) and vemurafenib (approved dose) in patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation.

On October 22, 2013, FDA issued an Advice/Information Request letter, which included the following advice:

- "Please be advised that you will need to demonstrate the relative contribution of each investigational product to the effect of the combination in an NDA submission seeking initial approval of two previously unapproved investigational products for use in combination. Data that is limited to clinical outcomes evaluating only LGX818 and MEK162 as single agents would not be sufficient to demonstrate the contribution of each component of the combination. Please refer to the FDA Guidance for Industry "Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination."

On April 9, 2014, a Type C teleconference was held between representatives of FDA and Novartis, to discuss proposed changes to the ongoing Phase 3 Study CMEK162B2301 with an emphasis on FDA's statements that the trial design, which employs a higher dose of encorafenib in the combination arm than the single-agent arm, would not allow an adequate assessment of the contribution of binimetinib treatment effect in the combination, that the proposal to present results from the primary efficacy analysis and immature results from the key secondary analysis without overall survival information would not provide sufficient information to file an NDA, and that the proposed Bayesian analysis was not acceptable to assess the treatment effects of the combination. Novartis stated that the dose of encorafenib could not be increased for reasons of unacceptable toxicity; FDA agreed to review this information.

On July 23, 2014, a Type C teleconference was held between representatives of FDA and Novartis, to discuss the ongoing going study, CMEK162B2301 and to obtain feedback on the encorafenib dosing rationale and the proposed modifications to the analysis plan. FDA reiterated the need for Novartis to demonstrate the relative contribution of each investigational product to the effect of the combination and that the proposed Bayesian analysis for estimating the contribution would be considered exploratory. The FDA further stated that an application in which substantial evidence of effectiveness has not been demonstrated would not be fileable. FDA recommended that Novartis add a treatment arm consisting of encorafenib 300 mg daily in combination with binimetinib 45 mg twice daily and compare that arm to the encorafenib single-agent arm to establish the contribution of binimetinib.

On November 20, 2014, Novartis submitted an amended protocol CMEK162B2301, Version 3, intended to address the FDA's concerns. In this amendment, Novartis added a Part 2 to the trial, in which additional patients would be randomized 3:1 to either encorafenib 300 mg daily in combination with binimetinib 45 mg twice daily or to encorafenib 300 mg daily as

monotherapy. In an advice letter, FDA stated that based on separate randomizations of patients in the single-agent encorafenib arm (Part 1 and Part 2) and the encorafenib 300 mg plus binimetinib 45 mg arm (Part 2 only), there may be some imbalance in important patient characteristics with potential introduction of bias.

On March 2, 2015, Novartis stated that Array BioPharma, Inc. (Array) regained worldwide rights to encorafenib and binimetinib from Novartis, and on September 15, 2015, Novartis transferred sponsorship of IND 113850, and all rights and responsibilities related to the IND application to Array.

On January 22, 2016, Array submitted a Type C, Written Responses Only meeting request to reach agreement on the clinical data plan, including the presentation of efficacy data and the pooling and presentation of clinical safety data, to support a planned NDA for encorafenib for use in combination with binimetinib for the treatment of patients with BRAF V600 mutation-positive melanoma. (FDA final written responses issued on April 7, 2016.)

On February 12, 2016, Array submitted a Type C, Written Responses Only meeting request to reach agreement with the Agency on the clinical pharmacology program and the presentation of clinical pharmacology data to support a planned NDA for encorafenib, for use in combination with binimetinib for the treatment of patients with BRAF V600 mutation positive melanoma. (FDA final written responses issued on April 26, 2016.)

On November 21, 2016, Array and FDA held an informal teleconference in response to a November 15, 2016, e-mail communication from Array requesting a meeting to discuss recent DMC recommendations to modify Part 2 of Study CMEK162B2301 and to determine whether the data are sufficient to support the encorafenib and binimetinib NDA filings. FDA stated that the higher dose of encorafenib in the combination arm as compared to the encorafenib single-agent arm confounds the assessment of the contribution of binimetinib to the effect of the combination.

On February 20, 2017, a Pre-NDA meeting was held with Array to discuss and reach agreement on the content and presentations of data for the NDAs to support the use of encorafenib in combination with binimetinib and binimetinib in combination with encorafenib in patients with BRAF V600 mutation-positive melanoma. The key points were:

- FDA did not agree that efficacy data from Part 1 of study CMEK 162B2301 would be adequate to demonstrate the contribution of binimetinib to the treatment effect of binimetinib when administered with encorafenib. In response, Array agreed to provide Part 2 data.
- FDA stated that based on the information available at the time of the pre-NDA meeting, FDA did not believe that a REMS would be necessary.
- FDA generally agreed with the proposed population PK analysis plan but noted that using population PK analysis to assess the impact of uncontrolled concomitant medication exposure is challenging.

On February 21 2017, a Pre-NDA meeting CMC only was held with Array to reach agreement with the FDA on the content and presentations of data for the NDAs to support the use of

encorafenib in combination with binimetinib and binimetinib in combination with encorafenib in patient with BRAF V600 mutation-positive melanoma.

On June 30, 2017, the NDAs were submitted electronically.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology Products 2 (DOP2) consulted the Office of Scientific Investigation (OSI) to perform an audit to support the review of the NDA applications. The focus of the inspection was Part 1 of COLUMBUS, and clinical investigator site selection was based accordingly. Four clinical sites were audited: Dr. Ivana Krajsova (clinical site 2013), Dr. Caroline Dutriaux (clinical site 3046), Dr. Ralf Gutzmer (clinical site 4015), and Dr. Thaddeus Beck (clinical site 5048). The Division selected these sites, in consultation with OSI, based on enrollment characteristics, patterns of protocol violations reported for the sites, patterns of efficacy reporting, and patterns of serious adverse event (SAE) reporting. The Contract Research Organization (CRO) responsible for some aspects of the clinical trial, (b) (4) was also audited.

The overall conclusion for the OSI inspection is that the data submitted to the FDA in support of COLUMBUS appear reliable based on available information from the inspection of the four clinical sites and the CRO.

There were no significant inspectional observations for clinical investigators Dr. Krajsova, Dr. Dutriaux, Dr. Guztmer, and the CRO. The final classification for the inspections of these sites is No Action Indicated (NAI). Regulatory violations were observed during the inspection of Dr. Beck. For this site, a Form FDA-483 was issued for, “Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigations.” Specifically, case histories, including the case report forms and supporting data, were not properly retained for the patients enrolled at the site, although the records were scanned and imported into ARIA and OncoEMR electronic medical records system. These violations were considered by OSI to be unlikely to significantly impact the determination of efficacy and safety, and the final classification for the inspection is Voluntary Action Indicated (VAI). OSI recommended that a sensitivity analysis with and without data from Site 5048 be performed; however, the clinical reviewer determined that as Site 5048 enrolled only 7 patients across three treatment arms of COLUMBUS, any impact of data from this site on the primary efficacy or safety analyses would be minimal.

4.2. Product Quality

Novel excipients: No

Any impurity of concern: No

Binimetinib drug product (MEKTOVI™) is presented a conventional immediate-release, film-coated, yellow to dark yellow, unscored biconvex ovaloid (capsule-shaped) tablet in a strength of 15 mg for oral administration. The tablet is debossed with a stylized “A” on one face and “15” on the opposite face.

The inactive ingredients are (tablet core): lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate (vegetable source), and (film coating): polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, ferric oxide yellow, and ferrosoferric oxide. All excipients are compendial grade. (b) (4) The proposed commercial tablet formulation is the same tablet formulation used in the pivotal clinical study and no significant changes to the manufacturing process have been made since the development of the manufacturing process used for production of batches for the pivotal clinical study. Thus, no formulation bridging is needed.

The tablets are packaged in 90 mL high density polyethylene (HDPE) bottles (b) (4) induction seal in a 180-ct presentation (for 3 tablets BID x 30 days). The drug product is labeled for storage at USP controlled room temperature. The provided stability data supports the proposed storage conditions in the working range of 20°C to 25°C with short term excursions down to 15°C and up to 30°C. The proposed shelf life of 36 months is acceptable based on the data provided in the application.

There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections. The applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31(b). Approval of the NDA was recommended by the Product Quality review team.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

The applicant is seeking an indication for patients with unresectable or metastatic melanoma limited to those who have a BRAF V600E or V600K mutation, which is the target of encorafenib. In COLUMBUS, patients were selected based on detection of a BRAF V600E and/or V600K mutation in tumor tissue prior to enrollment as determined by a sponsor designated central laboratory utilizing a bioMerieux ThxID™ BRAF assay. It was determined that a device to select patients for therapy would be required for the safe use of this drug when marketed. The applicant cross-referenced supplemental PMA application P120014 (S008) for the ThxID™ BRAF Assay Kit. At the time of completion of this review, the Center for Devices and Radiologic Health (CDRH) had not yet made a final regulatory determination for the PMA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Binimetinib (ARRY-162) is an orally bioavailable, slowly-reversible inhibitor of MEK1 and MEK2 kinases. In biochemical assays binimetinib inhibited MEK1 and MEK2 with inhibitory concentrations (IC_{50}s) of approximately 12 and 46 nM, respectively, approximately 83-fold and 9.5-fold, respectively, below the average peak total (bound+unbound) clinical exposure of 438.5 ng/mL achieved in patients treated at the twice daily oral dose of 45 mg. In cultured cells and in mouse tumor models harboring either BRAF- or NRAS-mutants, binimetinib exposure reduced cell proliferation and ERK activation. In mouse tumor models expressing BRAFV600E, binimetinib in combination with encorafenib inhibited tumor growth at a greater rate compared to either encorafenib or binimetinib alone. In addition, treatment with the combination of binimetinib and encorafenib in a mouse model implanted with BRAFV600E tumors resulted in longer term inhibition of tumor growth compared to either drug alone.

To assess the safety of binimetinib the applicant conducted GLP-compliant toxicology studies of up to 26 weeks in Sprague-Dawley rats and up to 9 months in cynomolgus monkeys. In general, the target organs of toxicity and the toxicities observed in rats and monkeys during the acute and chronic toxicity studies were similar except for a higher incidence and severity of toxicity in the acute studies, which were conducted using higher doses. In the long-term (26-week) rat study, animals received binimetinb daily by oral gavage at doses of 0, 1, 3, or 10 mg/kg; no treatment-related deaths occurred. Clinical observations in rats included broken or missing teeth and scabbed areas on the skin at doses of ≥3 mg/kg (approximately 10.7 times the clinical exposure of 2103 ng*hr/mL exposure achieved at the 45 mg twice-daily dose). The major target organ in rats was the skin, consistent with the severe dermatologic reactions reported clinically. There was also some evidence of renal toxicity in rodents characterized by an increased incidence of mineralization of the renal pelvis and tubules, which is consistent with findings of increased serum phosphorous as well as elevations in creatine kinase. Rhabdomyolyis has been reported clinically.

In the long-term (9-month) monkey toxicology study animals received binimetinib daily by nasogastric gavage at doses of 0, 0.2, 2, or 5 mg/kg for up to 273 days. One female monkey at the high dose level of 5 mg/kg (approximately 1.3 times the clinical exposure by AUC at 45 mg twice daily) was euthanized moribund on Day 155, due to mild to moderate inflammation and epithelial degeneration in the large intestine. Clinical signs in monkeys that survived to scheduled termination included watery feces at all doses but at higher frequency in the high dose group. The major target organ in monkeys was the gastrointestinal tract. Although neither binimetinib nor its major metabolite inhibited hERG current in hERG-expressing cultured cells, transient QTc prolongation was observed in conscious, telemetered monkeys following administration of a single oral dose of 10 mg/kg (120 mg/m^2). Peak exposures measured in this study were approximately 2.7-fold higher than those anticipated in patients when binimetinib is administered at a twice-daily dose of 45 mg. No significant changes in ECG parameters were

observed in the long-term toxicology study in the monkey using lead-2 ECGs. QTc prolongation has been reported clinically in patients treated with binimetnib in combination with encorafenib.

Binimetinib has an N-Desmethyl metabolite that inhibits MEK1 with similar potency as the parent compound (IC50 of 7 nM). This metabolite was present in humans at approximately 12.5% of the parent exposure, but was further metabolized in monkeys preventing measurable exposure. In rats, the exposure to this metabolite was only 0.7 to 1.5% of the parent exposure based on a single dose pharmacokinetic study and the applicant did not assess exposure to the active metabolite in longer term rat studies. Based on an exposure estimate for the metabolite of approximately 1% in rats and a maximum binimetinib AUC of 86.7 ug*h/mL in the long-term rat study, the estimated metabolite exposure in this study was 867 ng*hr/mL. The estimated human exposure to the metabolite at the AUC of 2103ng*hr/mL for binimetinib at the 45 mg twice daily would be 263 ng*hr/mL, suggesting that the rat study can provide some safety coverage for this metabolite. In addition, an FDA-initiated QSAR analysis of the metabolite predicted that the N-desmethyl metabolite is negative for bacterial mutagenicity. For these reasons, the safety assessment of the active N-desmethyl metabolite is considered adequate at this time for the proposed patient population.

To assess the potential developmental and reproductive toxicity of binimetinib the applicant conducted studies in Sprague-Dawley rats and New Zealand White Hra:(NZW)SPF rabbits. Rats were administered 0, 10, 30, or 100 mg/kg of binimetinib by oral gavage, once daily from gestation Days 6 to 17 while rabbits were administered 0, 2, 10, 20 mg/kg of binimetinib by oral gavage, once daily from gestation Day 6 to 18. Toxicokinetic assessments were not included in either study. Toxicokinetic comparisons in rats were based on data collected in the 28-day toxicology studies conducted using similar dose levels while comparisons in rabbits were based on data collected in a dose-range finding study in pregnant animals which included the 10 mg/kg dose level.

In pregnant rats, administration of binimetinib at doses of 30 mg/kg group (approximately 37 times the clinical exposure at 45 mg twice daily) or greater resulted in mild developmental delays characterized by decreases in fetal weight (and maternal gravid uterine weight) as well as increases in skeletal variations. In contrast, administration of binimetinib to pregnant rabbits resulted in clear maternal toxicity at the high dose of 20 mg/kg (estimated exposure less than 8 times the clinical exposure at 45 mg twice daily) with increases in maternal death, early delivery, and abortion. At binimetinib doses of 10 mg/kg, resulting in exposures approximately 5 times those in humans at the 45 mg twice daily dose, rabbits showed clear increases in post-implantation loss, decreased fetal body weights, and a small increase in the number of malformations. In litters from surviving dams treated at the 20 mg/kg binimetinib dose level, there were increases in fetal visceral malformations (up to 23% of fetuses) that included dilated aortic arch, constricted ductus arteriosus, discontinuous interventricular septum, and smaller than normal pulmonary trunk. Based primarily on data from the rabbit embryo-fetal development study and the drug's mechanism of action, a warning for embryo-fetal toxicity is included in the label for MEKTOVI.

Carcinogenicity studies were not conducted with binimetinib and are not required to support the use of a drug intended to treat patients with advanced cancer. Binimetinib (ARRY-438162) showed no genotoxic potential in the standard genetic toxicology battery. Because binimetinib (ARRY-438162) showed no genotoxic potential in the standard genetic toxicology battery and the lack of significant findings in male or female reproductive organs, no advice regarding male contraception is included in the label for MEKTOVI. Females are advised to use contraception for at least 30 days after the final dose of MEKTOVI due to embryo-fetal toxicity demonstrated in embryo-fetal development studies in the absence of genotoxicity. No studies were conducted or required to investigate the presence of binimetinib in milk. Because many drugs are secreted in milk, the label includes a warning not to breastfeed during treatment with MEKTOVI for (b) (4) days after the final dose based on a half-life of 2-4 hours. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of MEKTOVI in combination with encorafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.

5.2. Referenced NDAs, BLAs, DMFs

NDA 210496 for encorafenib; all pharmacology submitted to support the activity of binimetinib in combination with encorafenib were reviewed under the encorafenib NDA.

5.3. Pharmacology

Primary pharmacology

In a cell-free phosphorylation-inhibition study using recombinant, constitutively activated MEK1 and recombinant ERK, binimetinib inhibited production of phosphorylated ERK (pERK) with an IC_{50} of approximately 12 nM (Study 162-ENZ-1). Inhibition appeared to be time-dependent and slowly reversible in this study. The activity of a binimetinib metabolite (AR0426032) on inhibition of pERK was stated to be approximately 7 nM in this study; however, data demonstrating that conclusion were not provided. In addition, the applicant conducted a cell-free phosphorylation assay using wildtype (WT) MEK1 and MEK2 (Study 162-ENZ-3) proteins that were pre-incubated with binimetinib and WT BRAF prior to incubation with ERK. Binimetinib inhibited ERK phosphorylation by WT MEK1 and MEK2 with IC_{50s} of approximately 16 and 43 nM, respectively, in this assay, suggesting that binimetinib can block WT MEK1/2-mediated ERK activation.

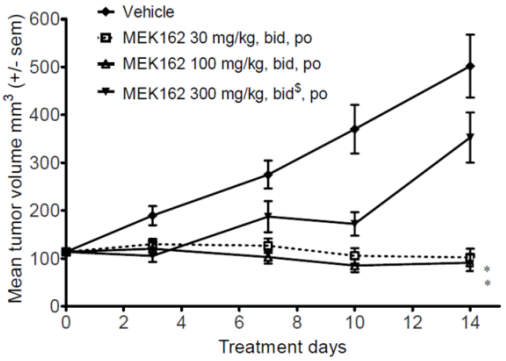
In cultured cells, binimetinib inhibited cell viability and pERK in a variety of N-Ras and BRAF-mutant melanoma cell lines (Report: RD-2010-00952), as summarized in Table 2. When these same studies were conducted with the combination of binimetinib plus the BRAF inhibitor, RAF265, improved cell-killing and pERK suppression was observed (data not shown).

Table 2: Summary of MEK162 potency data in cultured cells

Cell Line	Mutation(s)	Viability IC_{50} (nM)	pERK IC_{50}
A375	BRAF, CDKN2A	34.4 ± 9.3	27.4
RPMI-7951	BRAF, CDKN2A, PTEN, TP53	4359.1 ± 4717.6	125.8
IGR-1	BRAF, CDKN2A	372.2 ± 20.2	--
IGR-39	PTEN, TP53	9272.0 ± 1261.0	--
UACC-62	BRAF, CDKN2A, PTEN	34.1 ± 0.7	14.4
MDA-MB-435S	BRAF, CDKN2A, TP53	5046.6 ± 7005.2	--
Colo-800	TP53, CDKN2A	93.6 ± 28.2	7.6
WM-115	BRAF, PTEN, CDKN2A	99.8 ± 16.0	--
IPC-298	NRAS, TP53, CDKN2A	11.1	14.8
SK-MEL-30	TP53, CDKN2A	23.4	9.8
SK-MEL-2	TP53	71.7	5.3
MEL-JUSO	NRAS, HRAS, CDKN2A	149.5	3.9
Hs 944.T	NRAS, PTEN, CDKN2A	441.6	8.5

In female athymic nude mice (nu/nu) harboring BRAF-mutant A375 tumors, twice daily oral administration of 30 or 100 mg/kg binimetinib was associated with tumor growth suppression (report: RD-2010-00964). In contrast, a twice daily binimetinib dose of 300 mg/kg administered on an intermittent (3 days on/4 days off) schedule, was not fully active in this model (Figure 1).

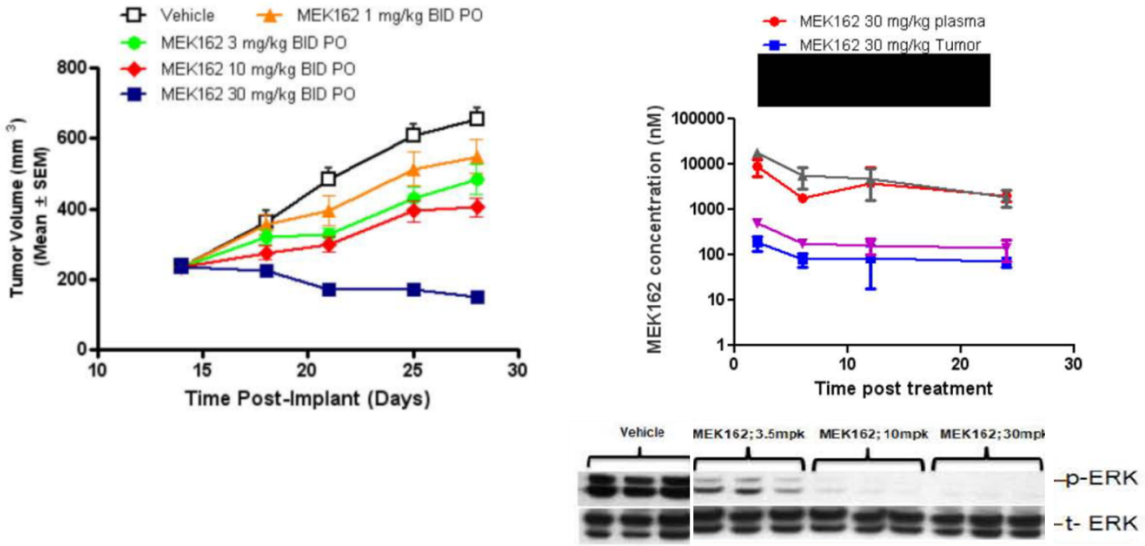
Figure 1: Activity of binimetinib in A375 melanoma xenografts in female nude mice



(Applicant Figure reproduced from Study #RD-2010-00964)

In female athymic nude (nu/nu) mice harboring NRAS-mutant Hs944T implants (Report: RD-2012-50080), twice daily oral binimetinib doses of 30 mg/kg were associated with tumor growth suppression (Figure 2, upper left panel). In a separate single-dose PK/PD study, binimetinib administration at twice daily doses of 10 and 30 mg/kg were associated with pERK suppression in tumors; however, no effect on total ERK (tERK) was observed (lower right panel). In this study, exposures in tumors were approximately 10-fold lower than those of plasma (upper right panel – the black bar reflects data redacted by the applicant that pertains to an irrelevant compound).

Figure 2: Summary of binimetinib repeat- (left) and single- (right) dose pharmacodynamic activity in an NRAS-mutant xenograft model



(Applicant Figure reproduced from Study #2012-50080)

Secondary Pharmacology

In a screen of over 200 protein kinases (Study: 162-Enz-2), binimetinib exhibited inhibition of MEK1 at 1 and 10 µM with little off-target activity. At 10 µM, Fer (fps/fes related tyrosine kinase) and CAMK4 (calcium/calmodulin kinase IV) were significantly inhibited (≥30% reduction in activity vs. control); however, there was no inhibition detected at 1 µM and at 10 µM, inhibition of these targets was still less than 50%, therefore, the clinical relevance of these findings is unclear, given the clinical Cmax of 438.5 ng/mL (~ 1 µM) in patients treated at the recommended 45 mg twice daily dose.

Table 3: Inhibition of Kinase Activity by binimetinib (% control activity)

Target	1µM	10µM
CAMK4	--	68%
Fer	--	62%
MEK1	39%	7%

Safety Pharmacology

The applicant performed a complete battery of safety pharmacology studies in Sprague-Dawley [Crl:CD®(SD)] rats to assess potential effects on pulmonary, CNS, renal, and GI functions. For each study, animals received a single oral dose (0, 10, 30 and 100 mg/kg) of binimetinib.

Animals designated for pulmonary evaluation (Study 1140-011; 12 males/Group; 8/Group for pulmonary evaluation, 4/Group for evaluation of blood gas parameters) were enclosed in

plethysmography chambers and monitored for tidal volume and respiratory rate for 4-hours post-dose. Animals designated for blood gas evaluation underwent arterial blood collection at 1 and 4 hours post-dose. There was no effect on respiratory rate or minute volume. Minor, non-dose-related variations in tidal volume were observed at the low-dose level (between 2-2.74 and 3.5-3.75 hours post-dose). There were no effects on any blood gas parameter measured (pH, pCO2, pO2, HCO2act, tCO2, tHb, FO2Hb, sO2, FCOHb, FMetHb). Given the absence of effects on minute volume (tidal volume X respiratory rate) and blood gas parameters, the significance of the decreased tidal volume in low-dose animals is unclear. The No Observed Effect Level (NOEL) was considered to be 100 mg/kg.

In the CNS safety pharmacology study, animals (Study 1140-012; 10/sex) underwent functional observational battery assessments (predose and at 1 and 24 hours post-dose). An additional 5 animals/sex underwent evaluation of locomotor activity using a Digiscan® activity monitor. An apparent treatment-related decrease in mean-body temperature was observed at 24 hours post-dose in all treated female groups. While a decrease in mean body temperature was also observed predose in the 30 mg/kg dose group in females, no change was observed at 1 hour post-dose. There were no other abnormal clinical signs, and no other dose-related effects on any endpoint assessed. The NOEL was considered to be 100 mg/kg.

To assess renal function (Study 1140-010), animals underwent blood and urine collection at 6 hours post-dose administration. Sporadic differences between controls and treated groups were occasionally noted for some serum chemistry parameters (~1% decrease in sodium and a ~ 3% increase in urea nitrogen) in treated groups vs. controls; however, the magnitude of the effects were small and there was no evidence of a dose-response; thus, the findings were considered unrelated to treatment. No effects on urine chemistry parameters were observed. The NOEL was considered to be 100 mg/kg.

In the GI motility assay animals (Study 110-013; 10/sex), received a charcoal suspension via oral gavage (10 mL/kg charcoal in 10% gum arabic and deionized water) at about 2 hours post-dose, and were euthanized 20 minutes later. Motility was assessed by measuring the distance the charcoal suspension had traveled across the terminal ileum. There were no effects of binimetinib on GI motility in this study. The NOEL was considered to be 100 mg/kg.

To assess the effect on gastric secretion, rats (Study AA30228; 10 males per group) received a single oral dose of binimetinib and underwent pyloric ligation 45 minutes later. After approximately 4 hours, the stomach was removed and gastric contents were measured. A non-dose-related reduction in gastric secretion and gastric acidity was observed.

Table 4: Effect of binimetinib or pentagastrin on gastric secretion volume and gastric pH in the anesthetized rat

	Vehicle	10 mg/kg	30 mg/kg	100 mg/kg	Pentagastrin	Water
Volume (µL)	377	245	181	382	754	308
pH	1.6	2.1	2.3	1.5	1.4	1.7

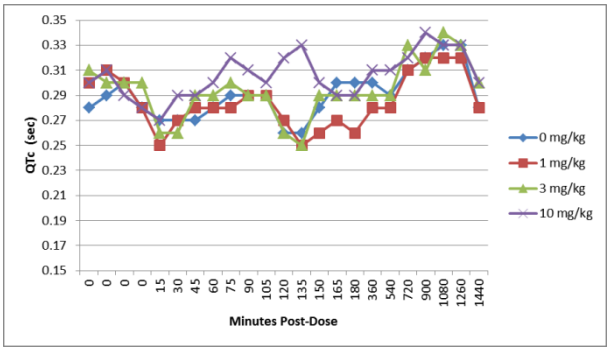
Vehicle: 1% CMC (w/v) / 0.5& Tween 80 in water for injection; Pentagastrin: 32 µg/kg

The effects of binimetinib and its pharmacologically active metabolite (AR00426032) were assessed on the human ether-à-go-go (hERG) gene in two separate whole cell patch clamp assays in cultured, hERG-transfected human embryonic kidney (HEK293) cells. Binimetinib (Report: 05726.BCP) inhibited the hERG current by 8% at 10 µM and 30.4% at 30 µM (the highest concentration tested); thus, the IC_{50} for hERG inhibition could not be established in this assay. AR00426032 (Report: PCS-141541) inhibited the hERG current by 3.4%, 7.9%, and 11.3% at 10, 30, and 100 µM respectively. These results suggest that neither binimetinib nor its metabolite pose a clinical risk of hERG inhibition in humans.

To assess the effects of binimetinib on cardiovascular function, the applicant performed a study in conscious, telemetered cynomolgus monkeys (Study JAY00033; N = 6 males). The drug was administered via the nasogastric route, and the study employed an escalating dose design. All animals received all doses (dose days were 1, 2, 7, 12 and 16 for the 0, 3, 10 and 10 mg/kg dose, respectively), and animals received the high dose twice due to a failure of the telemetry device on Day 12. Blood samples for TK were collected at 2 and 24 hours post-dose on Days 1, 2, 7, and 12. Statistical analyses were not conducted.

As shown in Figure 3, an increase in the QTc interval was observed in the high-dose monkeys between 75 and 150 minutes post-dose. Mean peak exposures (measured at 2 hours post-dose) in monkeys treated at the 10 mg/kg dose level in this study were 1.2 µg/mL (1200 ng/mL). Because statistical analyses were not performed, it is unclear whether this finding rises to the level of statistical significance. Given the small numbers of animals used and the fact that the finding occurred in high-dose animals during the period of maximal plasma exposure, an effect of binimetinib on the QT interval cannot be excluded.

Figure 3: Effect of binimetinib on the mean QTc interval in the male monkey



In addition to a potential prolongation of the QTc (Fridericia's) interval, binimetinib administration also led to an intermittent decrease in mean heart rate in high-dose animals between 40 and 540, and in mid-dose animals between 540 and 1040 minutes post-dose (data not shown). As the QTc interval is corrected for heart rate, these data do not affect the interpretation of data presented in Figure 3. Administration of binimetinib was also associated with a decrease in body temperature (~ 1.5 to 2^{o}C) between 40-540 minutes post-dose and an increase in mean body temperature (~ 1^{o}C vs. concurrent control) between 640-790 minutes post-dose in animals treated at the 10 mg/kg dose level (data not shown).

5.4. ADME/PK

Type of Study	Major Findings
Absorption Pharmacokinetics of ARRY-138162, AR00426032 (N-desmethyl metabolite), and AR00426618 (amide metabolite) in nude mice Following single intravenous or oral dose administration of binimetinib (Protocols 060302-1074 and 060302-1122). Report: DM09-043	***nu/nu* NCr mice** **Exposure to binimetinib:** • AUC_{inf} (30 mg/kg PO): 47,256 ng*hr/mL • C_{max} (30 mg/kg): 6,800 ng/mL • T_{max} (30 mg/kg): 2 hours • F%: 54 **Exposure to AR00426032 following administration of binimetinib** • AUC_{inf} (30 mg/kg): 7,858 ng*hr/mL • C_{max} (30 mg/kg): 1,462 ng/mL • T_{max} (30 mg/kg): 2 hours **Exposure to AR00426618 following administration of binimetinib** • AUC_{inf} (30 mg/kg): 26,172 ng*hr/mL • C_{max} (30 mg/kg): 2,200 ng/mL • T_{max} (30 mg/kg): 12 hours
Distribution Quantitative tissue distribution of drug-related material using whole-body autoradiography following a single oral dose of [^{14}C]Arry-438162 (30 mg/kg) to male Long-Evans and Sprague Dawley rats and human radiation dosimetry prediction Report: DM07-001	• No distribution to the CNS • binimetinib was broadly distributed into tissues. At Tmax (1 hr), the highest concentrations were observed in the blood, bile, kidney, urinary bladder, and GI tract. • Albino and pigmented rats generally showed similar patterns of distribution.
Metabolism In vitro and in vivo metabolism of ARRY-215311 Report: DM05-038	• The most abundant metabolite identified in this study was the glucuronide conjugate of binimetinib • No unique human metabolites were identified

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>DDI
[14C]MEK162: Metabolic profile in human hepatocytes and human liver microsomes, contributions of cytochrome
P450s and UDP-glucuronosyltransferase to metabolism, and potential for drug-drug interactions
Report: 1100166</td><td>• The major human metabolites identified in this study were an N-desmethyl metabolite and two glucuronide conjugates.
• The CYP enzymes involved in the metabolism of MEK162 were CYPs 1A1, 1A2, 2C19, and 3A4.
• Inhibitors of CYPs 1A1 and 2C19, and inhibitors of UGTs may lead to drug-drug interactions.</td></tr>
<tr><td>Excretion
Biliary excretion and metabolism in the rat after a single intravenous or oral dose of [^{14}C]MEK162 to bile-duct cannulated rats
Report: DMPK R1400168</td><td>• Following administration of an oral 4 mg dose, binimetinib-associated radiation was eliminated primarily in feces and bile (30% and 39.4%, respectively over 48 hours)
• Urinary elimination accounted for 20% of total radiation recovered during the 48 hour period.</td></tr>
<tr><td>TK data from general toxicology studies

A 28-Day Repeat-Dose Oral Toxicity Study of ARRY-215311 in Rats followed by a 4-Week Recovery
Report: 1140-007</td><td>TK data from long-term studies was incorporated in review of general toxicology studies in section 5.5.1

<table>
<tr><th></th><th></th><th colspan="2">10 mg/kg</th><th colspan="2">30 mg/kg</th><th colspan="2">100 mg/kg</th><th colspan="2">300 mg/kg</th></tr>
<tr><th></th><th>Parameter / Sex</th><th>Female</th><th>Male</th><th>Female</th><th>Male</th><th>Female</th><th>Male</th><th>Female</th><th>Male</th></tr>
<tr><td rowspan="7">Day-27</td><td>C_{max} (µg/mL)</td><td>6.05</td><td>4.55</td><td>11.2</td><td>8.00</td><td>14.6</td><td>12.9</td><td>NS</td><td>NS</td></tr>
<tr><td>T_{max} (hr)</td><td>0.5</td><td>0.5</td><td>0.5</td><td>4.0</td><td>0.5</td><td>4.0</td><td>NS</td><td>NS</td></tr>
<tr><td>$t_{1/2}$ (hr)</td><td>7.25</td><td>4.79</td><td>8.17</td><td>5.72</td><td>13.9</td><td>4.84</td><td>NS</td><td>NS</td></tr>
<tr><td>AUC_t (hr*µg/mL)</td><td>56.5</td><td>32.1</td><td>76.6</td><td>79.9</td><td>142</td><td>128</td><td>NS</td><td>NS</td></tr>
<tr><td>AUC_t / D (hr*kg*µg/mL/mg)</td><td>5.65</td><td>3.21</td><td>2.55</td><td>2.66</td><td>1.42</td><td>1.28</td><td>NS</td><td>NS</td></tr>
<tr><td>MRT_t (hr)</td><td>7.20</td><td>5.96</td><td>6.65</td><td>7.08</td><td>8.46</td><td>6.85</td><td>NS</td><td>NS</td></tr>
</table></td></tr>
<tr><td>TK data from reproductive toxicology studies

Range-Finding Study for Effects on Embryo-Fetal Development in New Zealand White Rabbits
Report: 1140-022</td><td>The applicant did not include TK data in the GLP-compliant reproductive toxicology studies. The same doses of binimetinib were used in the rat EFD and the 28-day GLP-compliant IND enabling studies.

The applicant conducted a dose range finding study in pregnant rabbits, which included TK, at doses of 10, 30, and 100 mg/kg binimetinib. 10 mg/kg was also used in the GLP-compliant study</td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: 26-Week Repeat-Dose Oral Toxicity Study of ARRY-438162 in Rats Followed by a 4-Week Recovery/ #1140-029

Key Study Findings

- No treatment-related mortalities
- Major target organs of toxicity include skin and kidneys along with some changes in bone marrow populations
- Increases in creatine kinase, phosphorus; histopathologic findings of renal tubular and pelvic mineralization at all doses, skin inflammation and erosion/ulceration at HD

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 1, 3, and 10 mg/kg* once daily for 13 weeks or 26 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	1% carboxymethylcellulose (CMC), 0.5% Tween® 80 in Sterile Water for Injection, USP
Species/Strain:	Crl:CD®(Sprague-Dawley) rats
Age:	8 weeks old
Deviation from study protocol affecting interpretation of results:	No

*Dose levels used in the study were informed by the multi-organ mineralization seen at all dose levels (low dose=30/10 mg/kg) in a 28-day toxicity study

Study Design

Group	Dose level (mg/kg)	Dose Volume (mL/kg)	Number of Animals							
			Male				Female			
Main Study			Wk 13		Wk 26		Wk 13		Wk 26	
			MS	Recov	MS	Recov	MS	Recov	MS	Recov
1	0	5	10	5	10	5	10	5	10	5
2	1	5	10	5	10	5	10	5	10	5
3	3	5	10	5	10	5	10	5	10	5
4	10	5	10	5	10	5	10	5	10	5
Toxicokinetics (TK)										
5	0	5	5				5			

Group	Dose level (mg/kg)	Dose Volume (mL/kg)	Number of Animals	
			Male	Female
6	1	5	10	10
7	3	5	10	10
8	10	5	10	10

MS – Main study group; Recov – Recovery group

Observations and Results:

Parameter		Major Findings					
Mortality		--	--	--	--	1 (D120)	1 (D177)
		Two females in the control group died (D78 & D123). One male in the toxicokinetic group treated with 10 mg/kg died (D55). None of the deaths was treatment-related.					
Clinical observations		• Broken/missing teeth at ≥3 mg/kg • Skin: pelage, scabbed area males and females at ≥3 mg/kg • Scabbing persisted in females at 10 mg/kg during the recovery period • Malocclusion, females at ≥3 mg/kg					
Body Weights		No remarkable findings					
Ophthalmoscopy		No remarkable findings					
% change from control		**1 mg/kg (Wk13/26)**		**3 mg/kg (Wk13/26)**		**10 mg/kg (Wk13/26)**	
		M	**F**	**M**	**F**	**M**	**F**
Hematology	NEUT	--	--	--	-/↑124	--	↑194/↑219
	MONO	--	-/↑30	--	-/↑48		↑77/↑99
	LUC	--	↓33/↑27	---/↓26	--/↑24	--/↑44	↑25/↑38
Clinical chemistry	PHOS	--	--	--	--	↑12/↑21	↑20/37
	BILI	-/↓31	--	-/↓19	--	-/↓19	--
	CK	↑112/-	-/37	--	-/↑45	↑69/-	-/↑60
	BUN	--	--	-/↑20	↑12/-	↑22/↑24	↑13/↑22
	CHOL	--	--	-/↓16	--	-/↓26	--

Toxicokinetics

- Exposure to binimetinib (C_{max} and AUC) increased with increasing doses in female and male rats and exposure in females was consistently higher than in males at all doses
- Repeated administration of binimetinib showed some accumulation at all doses.

		1 mg/kg		3 mg/kg		10 mg/kg	
Parameter	Day	Female	Male	Female	Male	Female	Male
C_{max} (µg/mL)	1	0.768	0.478	3.33	1.74	8.32	4.19
	27	1.08	0.753	5.05	2.02	9.60	5.85
	90	1.43	1.16	6.11	2.78	12.4	11.6
	180	2.00	1.37	7.24	2.93	14.5	6.35
T_{max} (hr)	1	0.5	1.0	0.5	1.0	2.0	0.5
	27	0.5	1.0	0.5	1.0	2.0	1.0
	90	0.5	0.5	0.5	1.0	1.0	4.0
	180	0.5	0.5	0.5	1.0	1.0	2.0
AUC_t [b] (µg-hr/mL)	1	5.35	3.34	18.0	9.89	70.4	39.9
	27	7.51	4.60	23.9	10.8	67.5	39.0
	90	11.4	6.74	29.5	15.9	86.7	77.9
	180	11.0	6.20	29.7	15.2	83.2	60.4

Parameter	Major Findings
Gross pathology	scabbing was observed in females at 10 mg/kg
Histopathology **Adequate battery:** Yes	See Table 5 • Skin findings of ulceration/inflammation • Minimal to mild renal tubular and pelvic mineralization • Minimal tubular mineralization persisted through the recovery period , especially in females

LD: low dose; MD: mid dose; HD: high dose.-: indicates reduction in parameters compared to control. % changes compared to control

Table 5: Rat Terminal Histopathology-(Week 26) and *Recovery (Week 30)*

Microscopic Findings		0		1 mg/kg		3 mg/kg		10 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	10/*5*	9/*5*	10/*5*	10/*5*	10/*5*	10/*5*	9/*5*	10/*4*
	Grade	Terminal (Week 27)/*Recovery (Week 30)*							
Bone Marrow, Femur									
Increased adipocytes	Minimal	5	5/*1*	6	8/*1*	10	9/*4*	9	3
Kidneys									
Mineralization, pelvic	Minimal	--	--	--	1	1/*2*	1	--	1
	Mild	--	--	--	1	1	--	--	--
Mineralization, tubular	Minimal	--	3/*3*	1	3/*2*	2	6/*4*	3/*1*	10/*4*
Prostate gland									
Infiltration, mononuclear cells	Minimal	--	[redacted]	1	[redacted]	4	[redacted]	1	[redacted]
	Mild	--	[redacted]	--	[redacted]	--	[redacted]	--/*1*	[redacted]
Skin									
Alopecia/Hypotrichosis	Minimal	--		2/*1*	--	--	--	--	--
	Mild	--	--	--	--	--	--	--	1
Bacterial colonies	Minimal	--	--	--	--	--	--	--	1
Erosion/Ulcer	Mild	--	--	--	--	--	1	--	3
	Moderate	--	--	--	--	--	1	--	4
Exudate, epidermal surface	Mild	--	--	--	--	--	1	--	3
	Moderate	--	--	--	--	--	1	--	4
Inflammation, chronic	Minimal	--	--	--	--	--	--	--	--/*1*
	Mild	--	--	--	--	--	1	--	3
	Moderate	--	--	--	--	--	1	--	4

Study title/ number: A 9-Month Toxicity Study of ARRY-438162 Administered by Nasogastric Intubation to Cynomolgus Monkeys, with a 3−Month Recovery Period/ # JAY00117

Key Study Findings:

- One monkey in the 5 mg/kg group died due to gastrointestinal tract toxicity
- Target organs of toxicity include gastrointestinal tract (inflammation of the mucosa and degeneration of the epithelia of several sections of the gastrointestinal tract), and skin (dry); increases in plasma phosphorous also occurred

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 0.2, 2, and 5 mg/kg once daily for 92 or 273 days (Weeks 13 or 36)
Route of administration:	Nasogastric gavage
Formulation/Vehicle:	1% carboxymethylcellulose/0.5% Tween® 80 in deionized water
Species/Strain:	Cynomolgus Monkey
Number/Sex/Group	3 main; 2 for recovery (for both 92 day and 274 timepoints)
Age:	Males: 1.5 to 4.5 years; Females: 1.7 to 3.6 years
Satellite groups/ unique design:	Main study animals used for TK; No 13-week sacrifice of mid-dose group—animals not included in the study

Group No.	Number of M/F	Dose Level (mg/kg)	Dose Volume (mL/kg)	Number Necropsied: Day 92	Day 120	Day 274	Day 365
1	10/10	0 (control)	5	2*/3	2/2	3/3	2/2
2	10/10	0.2	5	3/3	2/2	3/3	2/2
3	5/5	2	5	--	--	3/3	2/2
4	10/10	5	5	3/3	2/2	3/3	2/1**

M/F = males/females; -- = not applicable
*Monkey 1002 was found dead on Day 12.
**Monkey 4509 was euthanized humanely on Day 155.

Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameter	Major Findings

<table>
<tr><th>Parameter</th><th>Major Findings</th></tr>
<tr><td>Mortality</td><td>• One male monkey in the control group (Animal # 1002) was found dead on Day 12, due to cardiovascular shock (unrelated to treatment).
• One female monkey in the 5 mg/kg high dose group (Animal # 4509) was euthanized moribund on Day 155, most likely due to mild to moderate inflammation and epithelial degeneration in the large intestine</td></tr>
<tr><td>Clinical observations</td><td>• Incidences of watery feces were observed in all animals including controls but at higher frequency in males and females in the 5 mg/kg group.
• Dry skin was observed in 3/5 females at 2 mg/kg , 1/10 males and 3/10 females at 5 mg/kg</td></tr>
<tr><td>Body Weights</td><td>• No significant drug-related findings in body weight or food consumption</td></tr>
<tr><td>Ophthalmoscopy</td><td>• No remarkable findings</td></tr>
<tr><td>ECG</td><td>• No remarkable findings (ECG or blood pressure)</td></tr>
<tr><td></td><td>0.2 mg/kg | 2mg/kg | 5 mg/kg</td></tr>
<tr><td></td><td>M | F | M | F | M | F</td></tr>
<tr><td>Hematology
Neutrophils (Wk36)
Lypmphocytes (Wk36)
Monocytes (Wk36)</td><td>
↑36%
--
--</td><td>
↑83%
--
--</td><td>
↑178%
↓29%
--</td><td>
↑210%
↓26%
--</td><td>
↑199%
↓31%
↑69%</td><td>
↑175%
↓25%
↑20%</td></tr>
<tr><td>Clinical chemistry
Phosphorus (Wk36)
Creatinine (Wk36)
Triglycerides (Wk36)</td><td>
--
--
↑39%</td><td>
--
↑32%
--</td><td>
--
--
--</td><td>
--
--
--</td><td>
↑13%
--
↑27%</td><td>
↑19%
↑22%
↑34%</td></tr>
<tr><td>Toxicokinetics</td><td>• Exposure to binimetinib (C_{max} and AUC) increased with increasing doses in female and male monkeys
• There were no remarkable differences between exposures in females and males at all doses
• Repeated administration of binimetinib showed no evidence of accumulation
<table>
<tr><th>Parameter</th><th>Day</th><th>0.2 mg/kg</th><th>2 mg/kg</th><th>5 mg/kg</th></tr>
<tr><td rowspan="3">C_{max} (µg/mL)</td><td>1</td><td>0.025</td><td>0.296</td><td>0.581</td></tr>
<tr><td>90</td><td>0.017</td><td>0.207</td><td>0.322</td></tr>
<tr><td>270</td><td>0.015</td><td>0.215</td><td>0.354</td></tr>
<tr><td rowspan="3">T_{max} (h)</td><td>1</td><td>3.06</td><td>1.70</td><td>2.70</td></tr>
<tr><td>90</td><td>1.50</td><td>1.20</td><td>1.45</td></tr>
<tr><td>270</td><td>2.33</td><td>1.93</td><td>1.67</td></tr>
<tr><td rowspan="3">AUC_{0-24} (µg•h/mL)</td><td>1</td><td>0.233</td><td>1.93</td><td>4.47</td></tr>
<tr><td>90</td><td>0.208</td><td>1.52</td><td>2.66</td></tr>
<tr><td>270</td><td>0.202</td><td>1.60</td><td>2.75</td></tr>
</table></td></tr>
<tr><td>Organ Weights</td><td>No remarkable findings</td></tr>
<tr><td>Gross pathology</td><td>Gross pathologic finding of watery content was observed in the colon of 3/4 monkeys at 5 mg/kg.</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>See Table 6
• Findings limited primarily to inflammation/degeneration in the GI tract
• No recovery findings at either the interim or terminal sacrifice timepoints</td></tr>
</table>

LD: low dose; MD: mid dose; HD: high dose.

Table 6: Monkey Histopathological Findings

Microscopic Findings		0				0.2 mg/kg				2 mg/kg				5 mg/kg			
		M		F		M		F		M		F		M		F	
	Day	92	274	92	274	92	274	92	274	92	274	92	274	92	274	92	274
	Group Size	2	3	3	3	3	3	3	3	[redacted]	3	[redacted]	3	3	3	3	3
	Grade	Terminal+Preterminal															
Cecum																	
Hyperplasia, Lymphoid; follicle; submucosa	Minimal	2	–	–		–		–						1		–	
	Mild	1				1		2			1		1	–	1	3	
	Moderate								–		–						
Infiltrate, mononuclear cell; mucosa; diffuse	Minimal								–		–		–	–	1	1	--
	Mild										2		2	3	2	1	1
Hyperplasia; Mucosa; diffuse	Mild												1		2		
Inflammation, Neutrophilic; mucosa; multifocal	Minimal													1		1	
Degeneration, epithelium; lumen; multifocal	Minimal													2		1	1
	Mild													–	2	1	1
Colon																	
Hemorrhage; mucosa	Minimal	1	1	–	–	1	–	1	–				2	1	–	1	1
	Mild	–	–	–	–	–		1	2					–	–	–	–
Infiltrate, Mononuclear Cell; Mucosa; diffuse	Minimal					–	–		2		2		–	–	–	–	–
Infiltrate, Mixed Cell; Mucosa; diffuse	Mild					–	–	–	–		–		1	–	–	–	1
Degeneration; epithelium; lumen; multifocal	Minimal							–	–		–		–	1		1	1
	Mild							–	–		1		–	1	1	2	1
Liver																	
Infiltrate, Mixed Cell; parenchyma	Minimal	–	1			2		1					1	2		–	
	Mild	–	–			–					1			–		1	
Infiltrate, Mixed Cell; parenchyma	Mild	–	–	–	–	–	2	–	–		–		–	–	2	–	–
Infiltrate, Mononuclear Cell; periportal	Minimal	–	2	–	–	–		1					1	–		2	2
	Mild	–	–	–	–	–		–			1		1	1	–	–	1
Infiltrate, Mononuclear Cell; parenchyma	Mild						2								2		
Necrosis, Single Cell; Hepatocyte; multifocal	Minimal						–	–	–		1		–	–	–	–	–
Rectum																	
Hyperplasia, Lymphoid; follicle; mucosa	Mild						–	–	2		–		–	–	–	–	–
Hyperplasia, Lymphoid; follicle; submucosa	Minimal	1		1		1		2	–		–		–	–		1	
	Mild	–		2		2		1			1				2	2	
Infiltrate, Mononuclear Cell; mucosa; diffuse	Minimal	–	1	–		–		–						1	1	–	
	Mild	–		–		–		–						2		2	
Inflammation, Neutrophilic; mucosa; multifocal	Minimal	–				–								1		1	
	Mild	–		–		–		–						1		1	
Degeneration; epithelium; lumen; diffuse	Mild	–		–		–		–						1		1	
Degeneration; epithelium; lumen; multifocal	Minimal	–		–		–		–						1		–	
	Mild	–		–		–		–						1		–	

General toxicology; additional studies

The short-term 28-day GLP-compliant toxicity studies in rats and monkeys were reviewed in detail under IND [redacted] (b) (4) to support the initiation of clinical trials with binimetinib. These shorter term studies used higher doses of binimetinib (ARRY-438162) with rats receiving 0, 30/10, 100/30, or 300/100 mg/kg. The administration of 30, 100, or 300 mg/kg of binimetinib to rats for the first 3 days was inadvertent, and was corrected from Day 4. Two rats, one male (Day 5) and one female (Day 29) in the 300/100 mg/kg group died most likely due to multiorgan mineralization, including the heart and lungs. Mineralization of multiple organs including vascular tissue occurred at all dose levels tested and was not fully reversible during the recovery period. The skin was identified as a major target organ, with more severe findings in females than males, consistent with higher exposures in females. Toxicokinetic data from Day 28 of this study was used for dose comparisons between clinical exposures and estimated exposures from doses used in the rat embryofetal development study.

Monkeys received doses of 0, 1, 3, or 10 mg/kg. Two monkeys, one female (Day 14) and one male (Day 28), in the 10 mg/kg group were euthanized for humane reasons. Treatment-related histopathologic findings in these euthanized animals included inflammation and degeneration

or ulceration/necrosis of the cecum, colon, and rectum. The GI findings led to the deterioration in the health of these animals. In general, the target organs of toxicity and the toxicities observed in rats and monkeys during the acute and chronic studies were similar, except for the higher incidence and severity in the acute studies.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title/ number: Bacterial Reverse Mutation Assay/ #AB14DW.503.BTL
Key Study Findings:

- ARRY-215311 was negative in the Bacterial Reverse Mutation Assay

GLP compliance: Yes
Test system: *Salmonella typhimurium* TA1535, TA1537 TA98, TA100 and TA102 *Escherichia coli* WP2 *uvr*A; Concentration of ARRY-215311: 15-5000 µg/plate ± S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells
Study title/ number: In Vitro Mammalian Cell Gene Mutation Test (L5178Y /$TK^{+/-}$ Mouse Lymphoma Assay)/ #AB14DW.704.BTL
Key Study Findings:

- ARRY-215311 was negative in the L5178Y/$TK^{+/-}$ Mouse Lymphoma Mutagenesis Assay

GLP compliance: Yes
Test system: L5178Y/$TK^{+/-}$ mouse lymphoma cells, clone 3.7.2C; Concentration of ARRY-215311 75-300 µg/mL ± S9
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: Mammalian Erythrocyte Micronucleus Test/ # AB14DW.123M.BTL
Key Study Findings:

- ARRY-215311 was negative in the mouse micronucleus assay

GLP compliance: Yes
Test system: Male ICR mice were administered single oral doses of 500, 1000 or 2000 mg/kg of ARRY-215311 and were euthanized 24 h or 48 h after treatment.
Study is valid: Yes

ARRY-438162 showed no genotoxic potential in the standard genetic toxicology battery.

5.5.3. Carcinogenicity

Carcinogenicity studies were neither submitted nor required to support the use of binimetinib in patients with advanced cancer

5.5.4. Reproductive and Developmental Toxicology

Embryo-Fetal Development

Study title/ number: Study for Effects of ARRY-215311 on Embryo-Fetal Development in Rats

Key Study Findings:

- Decrease in body weight gain in treated pregnant rats compared to controls
- Fetal findings limited to decreases in fetal body weight and increased skeletal variations at doses ≥ 30 mg/kg

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 10, 30, or 100 mg/kg once daily from gestation day (GD) 6-17
Route of administration:	Oral gavage
Formulation/Vehicle:	1% CMC, 0.5% Tween® 80 in Sterile Water for Injection
Species/Strain:	Crl:CD® (Sprague-Dawley) rat
Number/Sex/Group:	25
Satellite groups:	None
Study Design:	Time-mated rats
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	One animal at the 30 mg/kg dose level was found dead on GD 13 likely due to dosing error
Clinical Signs	There were no remarkable clinical observations
Body Weights	There was a decrease in gestational body weight gain compared to control between Days 6-9 (10% at 10 mg/kg, 12% at 30 mg/kg and 17% at 100 mg/kg), however, subsequent loss in gestation body weight gain through Day 18 was ≤7% at the 100 mg/kg dose level
Necropsy findings • Cesarean Section Data	

	0	10 mg/kg	30 mg/kg	100 mg/kg
Pregnacy Index (%)	96	100	100	96
Number of females with viable fetuses for examination on GD 20	24	25	24	24
Number pregnant	24	25	25	24
Number not pregnant	1	0	0	1
Died while pregnant	0	0	1	0
The death of one female at the 30 mg/kg dose level was attributed to dosing error. One female each at the 10 mg/kg and 100 mg/kg dose levels did not get pregnant.				
Gravid uterine weight	69.6 g	--	--	↓10%
Mean Corporate Lutea	14.1	14.5	13.9	13.8
Mean implantation sites	12.4	12.5	12.5	12.3
Mean % preimplantation loss	11.4	13.0	9.4	9.8
Mean % postimplantation loss	6.6	7.9	4.8	10.4
Mean Litter size	11.5	11.5	11.9	11.0
Mean Early Resorptions	0.8	1.0	0.6	1.3
Mean Late Resorptions	0.1	0	0	0
Fetal Weight Change relative to control				
Male	4.09 g	--	↓8%	↓11%
Female	3.92 g	--	↓9%	↓12%

Necropsy findings

- Offspring

	0	10 mg/kg	30 mg/kg	100 mg/kg
Summary of Individual Fetal Skeletal Observations				
Number of Fetuses Evaluated	139	145	143	135
Cervical Vertebrae: Neural arch(es), Additional ossification center (Variation)				
Number of fetuses (%)	1(0.7)	1(0.7)	2(1.4)	4(3.0)
Ribs: Ribs, Absent (Malformation)				
Number of fetuses (%)	0	2(1.4)	0	0
Ribs, Rudimentary (Variation)				
Number of fetuses (%)	24(17.3)	31(21.4)	32(22.4)	22(16.3)
Ribs, Unilateral full rib (Variation)				
Number of fetuses (%)	0	0	3(2.1)	0
Skull: Hyoid, Not Ossified (Variation)				
Number of fetuses (%)	0	1(0.7)	12(8.4)	7(5.2)
Interparietal bone, Incompletely ossified (Variation)				
Number of fetuses (%)	0	0	0	2(2.5)
Sternum: Sternebrae, Misaligned (Variation)				
Number of fetuses (%)	0	2((1.4)	3(2.1)	3(2.2)
Sternebrae, Not ossified (Variation)				
Number of fetuses (%)	16(11.5)	43(29.7)	48(33.6)	72(53.3)
Summary Fetal Skeletal Observations				
Total Malformations				
Number of fetuses (%)	0	2(1.4)	0	0
Total Variations				
Number of fetuses (%)	41(29.5)	78(53.8)	100(70.0)	110(84.5)

LD: low dose; MD: mid dose; HD: high dose

Embryo-Fetal Development

Study title/ number Study for Effects of ARRY-215311 on Embryo-Fetal Development in New Zealand White Rabbits/ #1140-023

Key Study Findings:

- 6/23 dams in the 20 mg/kg group died during the study
- Dose-related increases in post-implantation loss at doses ≥ 2 mg/kg; abortions at doses of 10 and 20 mg/kg
- Decreases in fetal birth weight and visceral malformations at doses ≥ 10 mg/kg

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2, 10, or 20 mg/kg once daily from gestation Day 6 to 18

Route of administration: Oral gavage

Formulation/Vehicle: 1% carboxymethylcellulose (CMC), 0.5% Tween® 80 in Sterile Water for Injection, USP

Species/Strain: New Zealand White Hra:(NZW)SPF rabbits

Number/Sex/Group: 23

Satellite groups: None

Deviation from study protocol affecting interpretation of results: No

Study design: Time-mated rabbits

Observations and Results

Parameters	Major findings
Mortality	The death of 6 pregnant animals in the 20 mg/kg group was attributed to binimetinib
Clinical Signs	Thin bodies were observed in pregnant animals in the MD and HD groups, corresponding to decreased body weight gain in pregnant animals in the same groups.
Body Weights	Decreases in pregnant body weight gain were observed in the MD and HD groups.
Necropsy findings • Cesarean Section Data	

	0	2 mg/kg	10 mg/kg	20 mg/kg
Pregnancy index (%)	100	100	100	95.7
Number of females with viable fetuses for examination on GD 29	23	23	19	14
Number pregnant	23	23	23	22
Number not pregnant	--	--	--	1
Number of abortions	--	--	1	1
Early deliveries	--	--	--	1
Died while pregnant	--	--	3	6
The death of 3 pregnant animals at the 10 mg/kg dose level was attributed to dosing error while the death of the 6 pregnant animals at the 20 mg/kg dose level was attributed to binimetinib				
Gravid uterine weight	0.52 kg	--	↓25%	↓38%
Mean Corporate Lutea	10.5	10.5	9.9	10.4
Mean implantation sites	9.8	9.3	9.4	9.3
Mean % preimplantation loss	6.0	10.7	5.3	11.1
Mean % postimplantation loss	3.7	6.4	15.4	27.8
Mean Litter size	9.4	8.7	7.9	6.5
Mean Early Resorptions	0.2	0.4	0.5	1.3
Mean Late Resorptions	0.2	0.3	0.9	1.5
Fetal Weight Change relative to control				
Male	40.5 g	--	↓22%	↓26%
Female	39.4 g	--	↓15%	↓25%

Necropsy findings

- Offspring

	0	2 mg/kg	10 mg/kg	20 mg/kg
Summary of Individual Fetal VIsceral Observations				
Number of Fetuses Evaluated	217	199	151	91
Thoracic Cavity, Aortic arch, dilated (Malfotrmation)				
Number of fetuses (%)	1(0.5)	0	2(1.3)	6(6.6)
Ductus arteriosus, Constricted (Malformation)				
Number of fetuses (%)	0	0	1(0.7)	4(4.4)
Innominate artery, Absent (Variation)				
Number of fetuses (%)	1(0.5)	0	3(2.0)	1(1.1)
Interventricular septum, Discontinuous (Malformation)				
Number of fetuses (%)	1(0.5)	0	1(0.7)	7(7.7)
Pulmonary trunk, Smaller than normal (Malformation)				
Number of fetuses (%)	0	0	1(0.7)	4(4.4)
Right lung, Azygous lobe absent (Variation)				
Number of fetuses (%)	3(1.4)	2(1.0)	0	5 (5.5)
Subclavian artery, Retroesophageal (Variation)				
Number of fetuses (%)	0	2(1.0)	2(1.3)	1(1.1)
Summary Fetal Visceral Observations				
Total malformations				
Number of fetuses (%)	2(0.9)	0	5(3.3)	21(23.1)
Total Variations				
Number of fetuses (%)	4(1.8)	4(2.0)	5(3.3)	7(7.7)
Summary of Individual Fetal Skeletal Observations				
Number of Fetuses Evaluated	217	199	151	91
Hind Limbs: Talus not ossified (Variation)				
Number of fetuses (%)	0	1(0.5)	0	3(3.3)
Ribs: Ribs, Rudimentary (Variation)				
Number of fetuses (%)	52(24.0)	47(23.6)	43(28.5)	16(17.6)
Ribs, Unilateral full rib (Variation)				
Number of fetuses (%)	25(11.5)	25(12.6)	26(17.2)	10(11.0)
Skull: Hyoid Arch, bent (Variation)				
Number of fetuses (%)	3(1.8)	11(5.5)	13(8.6)	1(1.1)
Sternum: Sternebrae, fused (Malformation)				
Number of fetuses (%)	0	2(1.0)	1(0.7)	1(1.1)
Sternebrae, Misaligned (Variation)				
Number of fetuses (%)	0	1(0.5)	4(2.6)	0
Sternebrae, Not ossified (Variation)				
Number of fetuses (%)	34(15.7)	24(12.1)	26(17.2)	18(19.8)
Summary Fetal Skeletal Observations				
Total malformations				
Number of fetuses (%)	0	2(1.0)	1(0.7)	1(1.1)
Total Variations				
Number of fetuses (%)	114(52.5)	109(54.8)	112(74.2)	48(52.7)

LD: low dose; MD: mid dose; HD: high dose

5.5.5. Other Toxicology Studies

None.

Sachia Khasar, PhD
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6 Clinical Pharmacology

6.1. Executive Summary

The applicant seeks approval of binimetinib (MEKTOVI), in combination with encorafenib (BRAFTOVI), for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test. The proposed binimetinib dosage regimen is 45 mg orally twice daily (BID) in combination with 450 mg encorafenib once daily (QD), with or without food.

The Clinical Pharmacology Section of the NDA is supported by single and repeat dose pharmacokinetics (PK) studies of binimetinib in cancer patients with the following evaluations and analyses: dose-response (D-R) and exposure-response (E-R) relationships, population pharmacokinetics (popPK), potential QT/QTc prolongation, effect of food, renal impairment and hepatic impairment on binimetinib PK, and potential PK drug-drug interactions (DDI) mediated by UGT1A1 and binimetinib as CYP3A4 inducer.

In the food effect study, a standard high fat meal had no influence on binimetinib exposure, supporting the recommendation for administering binimetinib with or without food. The dedicated hepatic impairment study showed a two-fold increase in the binimetinib exposure in patients with moderate or severe hepatic impairment. Dose adjustment for patients with moderate or severe hepatic impairment is recommended based on the observed magnitude increase in binimetinib exposure and identified E-R relationship for safety. The popPK analyses identified that bilirubin is the only clinically important covariate influencing binimetinib PK. No clear association was found between binimetinib exposure and efficacy. Encorafenib in combination with binimetinib had better efficacy and safety profiles compared to encorafenib monotherapy. In the registration trial, patients who received Combo 450 or Combo 300 had a statistically significantly lower risk of grade 3/4 AE and dose adjustment and reduction compared to patients who received encorafenib monotherapy. From a mechanistic basis, this observed reduction in BRAF inhibition-related toxicities is hypothesized to be due to binimetinib as MEK inhibitor blocks paradoxical activation in the MAPK pathway when encorafenib as a BRAF inhibitor is administered alone.

Recommendations
The proposed dosage regimen of binimetinib 45 mg BID in combination with encorafenib 450 mg QD is supported by the overall clinical evidence in patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation and identified D-R and E-R relationships for efficacy and safety. From a Clinical Pharmacology standpoint, the NDA is approvable provided that the applicant and the FDA reach an agreement regarding the labeling language.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness†	Proposed dosage regimen is supported by D-R and E-R relationships for overall response rate (ORR), progression-free survival (PFS) and preliminary overall survival (OS).
General dosing instructions	45 mg binimetinib BID in combination with encorafenib 450 mg QD, taken orally with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Reduce binimetinib 45 mg BID to 30 mg BID in patients with moderate or severe hepatic impairment.
Labeling	• For patients with moderate (total bilirubin > 1.5 and ≤ 3 x ULN and any AST value) or severe (total bilirubin levels > 3.0 × ULN and any AST value) hepatic impairment, the recommended dose is 30 mg orally twice daily. • The proposed (b) (4) therefore, is not recommended.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

In healthy subjects, systemic exposure of binimetinib and the active metabolite M3 was approximately dose proportional over the dose range of 5 to 80 mg after single dose administration, and 5 to 60 mg QD after repeat dose administration. Following binimetinib 45 mg BID in cancer patients, the geometric mean (%CV) steady-state $AUC_{0\text{-}tau}$ was 2103 (38%) ng*h/mL. and C_{max} was 438 (54%) ng/mL. The geometric mean accumulation ratio was 1.3 following binimetinib BID dosing.

Absorption
The median t_{max} is 1.5 hours following administration of binimetinib 45 mg BID. In the formal three-period, cross-over food effect study, the administration of a single dose of MEKTOVI 45 mg with a high-fat, high-calorie meal (consisting of 150 calories from protein, 350 calories from carbohydrate, and 500 calories from fat) had no effect on binimetinib exposure.

Distribution
Binimetinib is 97% bound to human plasma proteins over the concentration range of 50 to 50,000 ng/mL. The blood-to-plasma concentration ratio is 0.63. The geometric mean (%CV) apparent volume of distribution (V_d/F) of binimetinib at steady-state is 70 L (28%) following binimetinib 45 mg BID.

Metabolism
Binimetinib is primarily metabolized through glucuronidation (61.2% via UGT1A1), N-dealkylation and amide hydrolysis (17.8% via CYP1A2 and CYP2C19). Unchanged binimetinib is

the most abundant radiolabeled component accounting for 60% of the total radioactivity AUC. The equal potent active metabolite AR00426032 (M3) accounts for 7.3% of total radioactivity AUC, which was consistent with the PK study result suggesting that the overall geometric mean ratio of M3 to binimetinib (MR_{AUC}) was 12.8%.

Excretion
Following a single 45 mg oral dose of ^{14}C-binimetinib, 62.3% (31.7% as unchanged binimetinib) of the radioactivity dose was recovered in the feces, while 31.4% (6.5% as unchanged binimetinib) was recovered in the urine.

Dose- and Exposure-Response Relationships
Encorafenib in combination with binimetinib had better efficacy and safety profiles when compared to encorafenib monotherapy. The confirmed overall response rate (ORR) is higher in combination therapy (65%) compared to monotherapy (50%) in both parts of the registration trial. Both combination regimens (Combo 450 and Combo 300) showed a statistically significant improvement in progression-free survival (PFS) compared to its randomized monotherapy. Preliminary analysis on overall survival (OS) also indicated that patients treated with Combo 450 had a statistically significantly lower risk of death compared to its randomized monotherapy.

In general, the safety profile in combination therapy is also better. Patients with Combo 450 or Combo 300 had a statistically significantly lower risk of grade 3/4 AE and dose adjustment and dose reduction compared to patients with the monotherapy. In addition, patients with the combination therapy had significantly lower risks of developing grade 2+ myopathy, grade 2+ hand-foot syndrome, grade 2+ rash compared to patients with the monotherapy. On the other hand, the risks of experiencing definite deterioration in LVEF and grade 1+ retinopathy excluding retinal vein occlusion (RVO) were higher in the combination therapy groups.

No clear association was found between binimetinib exposure and ORR, PFS based on 449 patients treated with 45 mg BID in combination with encorafenib. A statistically significant relationship was found between time to OS and binimetinib Cmax, but such relationships were not observed on Cmin and AUC. The E-R relationship for safety was consistent with D-R relationship. Patients with lower binimetinib exposure had significantly lower risks of experiencing dose adjustment and dose reduction compared to patients with higher binimetinib exposure. On the other hand, patients with lower binimetinib exposure had significantly higher risks of experiencing serious adverse events and grade 2+ hand-foot syndrome compared to patients with higher binimetinib exposure.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen of binimetinib is 45 mg orally BID, with or without food. Dose selection was based on results of dose-finding studies. Study ARRAY-162-111 identified a

maximum tolerated dose (MTD) of 60 mg BID in patients with advanced or metastatic solid tumors, but was later reduced to 45 mg BID in the dose-expansion part of the study due to occurring ocular adverse events. Study CMEK162X2201 evaluated 45 and 60 mg BID in melanoma patients and the results re-confirmed 45 mg BID as the tolerated dose. The efficacy and safety of binimetinib was studied in the registration Study CMEK162B2301, in which binimetinib 45 mg BID was administrated in combination with encorafenib 450 mg QD in part 1 (Combo 450) and in combination with encorafenib 300 mg QD (Combo 300) in part 2. The contribution to the therapeutic effect by binimetinib was evaluated by the part 2 of the study, in which median PFS was increased by 3 months (12.9 months in Combo 300 vs. 9.2 months in encorafenib 300 mg, HR = 0.77, p=0.015) with ORR of 66% in Combo 300 and 50% in encorafenib 300 mg. Assessment of the safety data does not reveal any serious adverse reactions. Most of the adverse events were Grade 1 or Grade 2 in severity, were manageable either through dose interruption or dose reduction and did not lead to treatment discontinuations in the vast majority of cases.

Dose Reductions

Adverse Event Management

In the event of adverse reactions, binimetinib dose will be reduced to the lowest acceptable dose of 30 mg BID. The dose reduction schema is supported by the minimally effective binimetinib dose resulting in mean steady-state AUC that exceeds the effective AUC shown in nonclinical studies.

When binimetinib dose is reduced to 30 mg BID, encorafenib dose should remain the same. If binimetinib is permanently discontinued, encorafenib dose should be reduced from 450 mg once daily to 300 mg once daily. (b) (4)

Therapeutic Individualization

Hepatic Impairment (HI): In a dedicated study (CMEK162A2104), moderate (total bilirubin > 1.5 and ≤ 3 x ULN and any AST value) and severe (total bilirubin levels > 3.0 × ULN and any AST value) hepatic impairment cohorts showed increased binimetinib systemic exposure by 80% (90% C.I. of AUC ratio: 1.5, 2.3) and 110% (90% C.I. of AUC ratio: 1.7; 2.7), respectively compared to the normal hepatic function cohort. The recommended dose reduction of binimetinib in patients with moderate and severe HI is from 45 mg BID to 30 mg BID.

Summary of Labeling Recommendations

Hepatic Impairment (HI): Reduce the binimetinib dose to 30 mg BID in patients with moderate and severe HI.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

After a single and repeated dose in healthy subjects, systemic exposure of binimetinib and the active metabolite M3 was approximately dose proportional over the dose range of 5 to 80 mg after single dose administration and 5 to 60 mg QD after repeat dose administration.

Single and repeat dose binimetinib exposures as a single agent are shown in Table 7.

Table 7: Binimetinib Exposures after a Single and Repeat Doses of Binimetinib as a Single Agent in Study ARRAY-162-111

	Single Dose		Repeat Doses	
	Geometric Mean $AUC_{0\text{-}8h}$, ng·h/mL (%CV)	**Geometric Mean C_{max}, ng/mL (%CV)**	**Geometric Mean $AUC_{0\text{-}8h,ss}$ ng·h/mL (%CV)**	**Geometric Mean $C_{max,ss}$ ng/mL (%CV)**
ARRAY-162-111				
30 mg BID	1000 (34.0%) n=4	327 (28.6%) n=4	NA (NA)	417 (39.9%) n=4
45 mg BID	964 (28.4%) n=4	241 (43.2%) n=4	1490 (NA) n=4	273 (64.7%) n=4
60 mg BID	1710 (23.9%) n=7	545 (32.3%) n=7	1820 (14.4%) n=7	512 (30.8%) n=7
60 mg BID (Expansion)	1090 (293%) n=7	365 (141%) N=7	3760 (NA) n=7	594 (68.8%) n=7
80 mg BID	2220 (78.9%) n=4	687 (66.6%) n=4	NA (NA)	NA (NA)
CMEK162X1101				
15 mg Single Dose	762 (20.5%) n=6	202 (33.8%) n=6	NA (NA)	NA(NA)
30 mg BID	1750 (42.2%) n=6	443 (62.9%) n=6	2430 (38.3%) n=6	400 (41.9%) n=6
45 mg BID	1970 (29.2%) n=6	538 (32.2%) n=6	3550 (27.7%) n=6	771 (31.0%) n=6

Source: ARRAY-162-111 Study Report, Tables 14, Pages 145; CMEK162X2110 Study Report, Table 11-6, 11-7, Page 98.

Single and repeat dose binimetinib exposures in combination with encorafenib are shown in Table 8.

Table 8. Binimetinib Exposures after a Single and Repeat Doses of Binimetinib in Combination with Encorafenib in Study CMEK162X2110 and CMEK162X2201

	Single Dose		Repeat Doses	
	Geometric Mean $AUC_{0\text{-}24h}$, ng·h/mL (%CV)	Geometric Mean C_{max}, ng/mL (%CV)	Geometric Mean $AUC_{0\text{-}24h,ss}$ ng·h/mL (%CV)	Geometric Mean $C_{max,ss}$ ng/mL (%CV)
CMEK162X2201				
45 mg BID	1648 (35%) n=7	458 (46.1%) n=23	2102.9 (38.4) n=7	438.5 (53.9%) n=22
60 mg BID	1587.5 (37.8%) n=8	542.5 (33.0%) n=8	2637.5 (20.8) n=4	531.3 (49.0%) n=6

Source: CMEK162X2110 Study Report, Table 11-6, 11-7, Page 98;

A summary of general pharmacology and PK characteristics of binimetinib is shown in Table 9.

Table 9. Summary of General Pharmacology and Pharmacokinetic Characteristics of Binimetinib

Pharmacology	
Mechanism of Action	Binimetinib is an ATP-uncompetitive inhibitor of MEK1 and MEK2. In cell-free systems, binimetinib inhibits MEK1 and MEK2 with IC50's of 12 and 46 nM, respectively, on purified enzymes.
Active Moieties	Unchanged Binimetinib (~60%) and its equipotent metabolite M3 (<20% of binimetinib exposure) were the major circulating components at steady-state.
QT Prolongation	Based on FDA's QT-IRT review of a pooled data across 7 clinical studies, a relatively flat concentration - ΔQTcF relationship was observed for binimetinib or active metabolite M3. No large QTc prolongation (>20 ms) was estimated following 45 mg BID. The QT-IRT team focused on data from Studies ARRAY-162-111 and CMEK162A2301 for central tendency sensitivity analysis because ARRAY-162-111 included the supratherapeutic dose of 60 mg BID and CMEK162A2301 was the large pivotal trial. Additionally, both studies had replicate ECG measurements around T_{max} at steady state. For the central tendency analysis, no large QTc prolongations were observed at 45 or 60 mg BID (largest upper bounds of the 2-sided 90% CIs for mean ΔQTcF < 20 ms). Assay sensitivity could not be established, due to the lack of a positive control (moxifloxacin).
General Information	
Bioanalysis	Concentrations of binimetinib and its active metabolite (M3, catalyzed by CYP1A2 and CYP2C19 and equipotent to the parent) in human plasma, urine, dialysate were determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The validated bioanalytical methods used throughout binimetinib clinical development are summarized below in Table 10. The lower limit of quantitation (LLOQ) in plasma was improved from 5 ng/mL (Methods A and B) to 1 ng/mL (Methods C and D). Selectivity, accuracy, precision, sensitivity, recovery, reproducibility, stability were assessed as appropriate.

Healthy vs. Patients	Based on pooled population PK covariate analysis, a 32% greater CL/F in healthy subjects than that in patients was found.
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	Following binimetinib 45 mg BID in patients, geometric mean (%CV) $AUC_{0\text{-}tau}$ was 2,103 ng*h/mL (38%) and Cmax was 438 ng/mL (54%).
Range of Effective Dose or Exposure	Efficacy in nonclinical tumor models has been demonstrated at 1 mg/kg and with reproducible and robust effects at ~ 3 mg/kg (AUC_{inf} = 3.7 mcg*hr/mL), comparing to the exposure in humans at the 45 mg BID dose level with $AUC_{0\text{-}12h}$ range: 2.1 to 3.6 mcg*hr/mL
Maximally Tolerated Dose or Exposure	The MTD of binimetinib was determined to be 60 mg BID in the dose-escalation phase following a 3+3 dose-escalation design in study ARRAY-162-111. The dose for expansion phase was subsequently decreased to 45 mg BID due to the frequency of ophthalmic toxicity at the MTD.
Dose Proportionality	The exposures of binimetinib and its active metabolite M3 were dose proportional after single dose over the range of 5 to 80 mg (slope of 0.93 [90% CI: 0.75, 1.1] for $AUC_{0\text{-}8h}$ and 0.91 [90% CI: 0.67, 1.1] for C_{max}) and multiple dose over the dose range of 5 to 60 mg QD (slope of 0.98 [90% CI: 0.82, 1.1] for $AUC_{0\text{-}tau}$ and 1.1 [90% CI: 0.85, 1.2] for C_{max}).
Accumulation	The geometric mean accumulation ratio following binimetinib 45 mg BID was 1.3-1.5 fold.
Variability	Following binimetinib 45 mg BID, the inter-subject variability (CV%) for steady-state $AUC_{0\text{-}tau}$ was 38% and for C_{max} was 54%.
Absorption	
Bioavailability	The relative bioavailability of binimetinib when administered as 3 x 15 mg (b) (4) film-coated tablets was similar to that when administered as 3 x 15 mg film-coated tablets. The GMR and the 90% CIs for AUC_{inf}, AUC_{last}, $AUC_{0\text{-}72h}$ and C_{max} were within the (0.8, 1.25) boundaries for bioequivalence.
T_{max}	Following binimetinib 45 mg BID, the median t_{max} is 1.5 hours with the range of 0.4 to 8 hours.
Food effect (High fat meal/fasted)	• Effect of food on the bioavailability of binimetinib was evaluated in a three-period, six-sequence, crossover study, n=12 each for fasted, low-fat low-calorie and high-fat high-calorie cohorts. A high-fat meal consists of approximately 1000 calories (150 calories from protein, 350 calories from carbohydrates, and 500 calories from fat).
	$AUC_{0\text{-}\infty}$ | C_{max} | $T_{max(difference)}$
	Geometric Mean Ratio [90% CI] 0.99 [0.93, 1.1] | Geometric Mean Ratio [90% CI] 0.83 [0.71, 0.96] | Geometric Mean Ratio [90% CI] 1.03 [-3.25, 3.52]
Distribution	
Volume of Distribution	Following binimetinib 45 mg BID, the geometric mean (%CV) apparent volume of distribution (V_z/F) at steady-state was 70 L (28%).
Plasma Protein Binding	Binimetinib is 97% bound to human plasma proteins and the binding is not concentration-dependent over the range of 50-10000 ng/mL in vitro.
As Substrate of Transporters	• Substrate of p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). • Not a substrate of uptake transporter families (OCT1, OATP1B1, OATP1B3, OATP2B1). Due to the minimal biliary elimination and moderate to high permeability, the potential for involvement of P-gp and BCRP in the biliary excretion or absorption of binimetinib is low.

<table>
<tr><th colspan="4">Elimination</th></tr>
<tr><td>Terminal Elimination Half-Life</td><td colspan="3">The mean elimination half-life ($t_{1/2}$) of binimetinib at steady-state was 7.4 hours in healthy subjects. Clearance (CL/F) in healthy subjects is 30% higher than in a typical patient, based on population PK analysis. Following oral administration of binimetinib 45 mg BID, the mean (%CV) apparent oral clearance (CL/F) of binimetinib at steady-state is 20 L/h (24.1%) in cancer patients.</td></tr>
<tr><td>Effective Elimination Half-Life</td><td colspan="3">The effective $t_{1/2}$ is the terminal elimination $t_{1/2}$, which is 7.4 hours.</td></tr>
<tr><td colspan="4">Metabolism</td></tr>
<tr><td>Fraction Metabolized (% dose)</td><td colspan="3">Based on the mean percentage of the dose recovered as metabolites in the excreta, the fraction metabolized is 56%.</td></tr>
<tr><td>Primary Metabolic Pathway(s)</td><td colspan="3">The major metabolic pathway of binimetinib is glucuronidation. The relative contributions of the glucuronidation, hydrolysis, and the oxidative pathways to overall binimetinib metabolism in human hepatocytes were 45%, 5% and 2.4%, respectively.</td></tr>
<tr><td colspan="4">Excretion</td></tr>
<tr><td>Primary Excretion Pathways (% dose) ±SD</td><td colspan="3">• Feces: 62.3% ± 4.4% (31.7% unchanged).
• Urine: 31.4% ± 3.7% (6.5% unchanged).</td></tr>
<tr><td colspan="4">Interaction liability (Drug as Victim)</td></tr>
<tr><td>Inhibition/Induction of Metabolism</td><td colspan="3">• There was no apparent relationship between binimetinib exposure and UGT1A1 mutation status genotype or smoking status (a UGT1A1 inducer). Simulations to investigate the effect of a UGT1A1 inhibitor (400 mg atazanavir) (UGT1A1 inhibitor) on the exposure of 45 mg binimetinib predicted similar binimetinib C_{max} in the presence or absence of atazanavir, the UGT1A1 inhibitor. The potential of drug interactions mediated by UGT1A1 is minimal.</td></tr>
<tr><td>Inhibition/Induction of Transporter Systems</td><td colspan="3">• The potential for involvement of P-gp and BCRP in the biliary excretion or absorption of binimetinib is low, due to the minimal biliary elimination and moderate to high permeability. No in vivo drug interaction study was conducted to assess the interaction potential.</td></tr>
<tr><td>Effect on Absorption
(binimetinib alone/with rabeprazole)</td><td colspan="3">• Effect of rabeprazole, a proton pump inhibitor (PPI), on the PK of binimetinib was evaluated in a 2-arm, parallel-group, fixed-sequence study, n=15 each for binimetinib alone and with rabeprazole cohorts. PK profiling of single dose binimetinib 45 mg was compared to that when given concomitantly with rabeprazole after a lead-in period of 4 days of rabeprazole 20 mg once daily (QD).
• Coadministration of rabeprazole had no effect on the $_{Tmax}$, AUC of binimetinib and M3 after a single dose of binimetinib 45 mg was coadministered. $_{Cmax}$ values of binimetinib and M3 were 17% and 24% lower, respectively in the presence of rabeprazole. However, the differences were within the intersubject variability and not considered clinically important
<table>
<tr><th>$AUC_{0-\infty}$</th><th>C_{max}</th><th>$T_{max(difference)}$</th></tr>
<tr><td>Geometric Mean Ratio
[90% CI]
1.04
[0.93, 1.17]</td><td>Geometric Mean Ratio
[90% CI]
0.83
[0.7, 0.98]</td><td>Geometric Mean Ratio
[90% CI]
0
[-0.5, 0.66]</td></tr>
</table></td></tr>
<tr><td colspan="4">Interaction liability (Drug as Perpetrator)</td></tr>
</table>

<table>
<tr><td>Inhibition/Induction of Metabolism</td><td colspan="3">

To effects of oral binimetinib on the PK of a sensitive CYP3A4 substrate (midazolam) was investigated in a single-arm, three-period, fixed-sequence cross-over study. PK profile of a single oral dose of midazolam 4 mg given before and after oral binimetinib 30 mg bid given for 7 and 15 days were evaluated and compared. The results suggested that binimetinib did not alter the exposure of midazolam (see table above, midazolam PK before vs that after binimetinib 30 mg bid for 15 days).
It is not expected for binimetinib to have a clinically relevant induction of CYP2C9, as the plasma concentrations observed in patients is well below the concentration required for minimal induction of CYP2C9 based on in vitro study.
Binimetinib is a weak inhibitor of human liver microsomal UGT1A, with an IC_{50} value greater than 25 µM.

<table>
<tr><td>$AUC_{0-\infty}$</td><td>C_{max}</td><td>$T_{max(difference)}$</td></tr>
<tr><td>Geometric Mean Ratio
[90% CI]
1.1
[0.98, 1.24]</td><td>Geometric Mean Ratio
[90% CI]
0.93
[0.75, 1.14]</td><td>Geometric Mean Ratio
[90% CI]
0
[-1, 1]</td></tr>
</table>
</td></tr>
<tr><td>Inhibition/Induction of Transporter Systems</td><td colspan="3">

Binimetinib is unlikely to increase the systemic exposure of co-medications with clearance is mainly mediated by OCT1 or OCT2 as binimetinib (1 to 100 µM) was shown to be a weak inhibitor of the transport activity of OCT2 (IC50 18.1 µM) and did not inhibit the transport activity of OCT1 in vitro.

</td></tr>
</table>

* PK parameters are presented as geometric mean (%CV) or median (minimum, maximum) unless otherwise noted.

The validated bioanalytical methods used throughout binimetinib clinical development are summarized below in Table 10. Selectivity, accuracy, precision, sensitivity, recovery, reproducibility, stability were assessed as appropriate. Recovery for binimetinib was > 80%, and ranged 37-39% with method B and ranged 84-89% with Method D for the metabolite M3. Stock solution stability, post-preparation stability and freeze/thaw stability met acceptance criteria within the ranges of the validated methods. Binimetinib and M3 in plasma are stable for up to 37 months when stored below -70 degrees and for up to 67 months when stored at -20 degrees. In human whole blood, binimetinib and M3 are stable at 4 degrees for up to 2 hours. Binimetinib in dialysate is stable for up to 5 months when stored at -18 degrees or below -70 degrees. Binimetinib in urine is stable for up to 96 days when stored at either -20 degrees or -80 degrees.

Table 10. Summary of analytical methods used in binimetinib clinical studies

Analytes	**Matrix**	**Method**	LLOQ (ng/mL)	Method Validation Report	Clinical Study
Binimetinib and AR00426032	Plasma	A	5	AA32830-01	ARRAY-162-0601 ARRAY-162-0602
Binimetinib and AR00426032	Plasma	B	5	234-0703	ARRAY-162-104 ARRAY-162-111 CMEK162X1101 CMEK162X2201
Binimetinib and AR00426032	Plasma	C	1	231-1207	CMEK162A2102 CMEK162A2101J

Binimetinib and AR00426032	Plasma	D	1	12BAS0106	ARRAY-162-105 ARRAY-162-106 ARRAY-162-311 CMEK162A2103 CMEK162A2104 CMEK162A2301
Binimetinib	Dialysate	E	0.5	15BAS0448	ARRAY-162-106 CMEK162A2104
Binimetinib and AR00426032	Urine	F	1	15BAS0401	ARRAY-162-106

Source: Table 1-2 in Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods

6.3.2. Clinical Pharmacology Questions

Is dose adjustment for binimetinib in patients with hepatic impairment necessary?

In the dedicated hepatic impairment study (Study CMEK162A2104), subjects with moderate and severe HI had 80% and 110%, respectively, higher binimetinib AUC than subjects with normal hepatic function (see Table 11 and Figure 4). A linear conversion of dose reduction from 45 mg BID to 30 mg BID predicts that the binimetinib exposure in patients with moderate or severe hepatic impairment will be similar to that of 45 mg BID in patients with normal hepatic function.

E-R analyses for safety by pooling data from 526 patients receiving binimetinib single agent from studies CMEK162A23013, CMEK162X22015, CMEK162X11016, and ARRAY-162-1117, shows that the incidence of retinal events of any grade, the incidence of Grade 3-4 CK increase, and the incidence of Grade 2+ LVEF decrease, are significantly higher with higher binimetinib exposure (Figure 5). These AEs resulted in dose withholding/interruption. In the registration trial, 58% of patients experienced Grade 3/4 AEs with 33% of patients requiring dose interruption and additional therapy, 34% of patients experienced SAEs with the binimetinib and encorafenib combination treatment. Dose adjustment recommendations for patients with moderate or severe hepatic impairment is based on exposure matching to minimize the risk of the above AEs that lead to dose interruptions (Figure 6).

Table 11. Dose-Normalized AUCinf Ratio (90% CI) and Cmax Ratio (90% CI) in Hepatic Impairment study CMEK162A2104

	AUC_{inf}_D (h*ng/mL/mg)	C_{max}_D (ng/mL/mg)
Mild HI (n=6) vs. Normal (n=10)	1.02 (0.816, 1.28)	1.07 (0.805, 1.41)
Moderate HI (n=6) vs. Normal (n=10)	1.81 (1.45, 2.27)	1.32 (0.999, 1.75)
Severe HI (n=6) vs. Normal (n=10)	2.11 (1.66 2.68)	1.57 (1.16, 2.11)

Source: CMEK162A2104 Study Report, Table 14.2.3.1.1, page 158.

Figure 4. Dose-Normalized Binimetinib Exposure

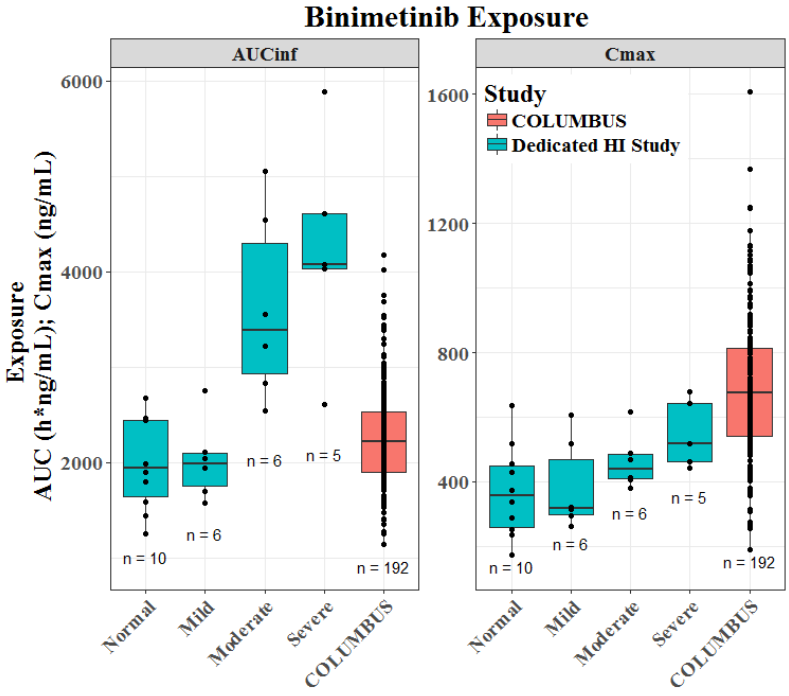
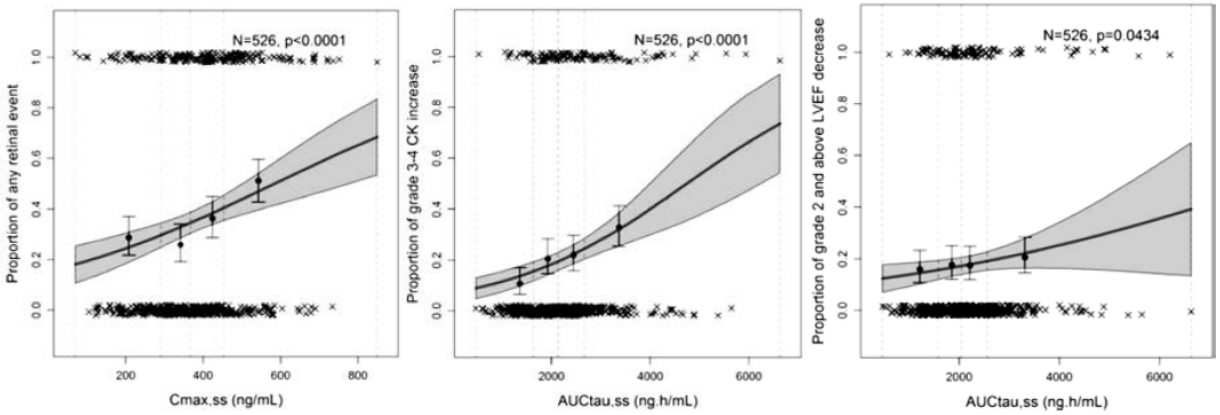
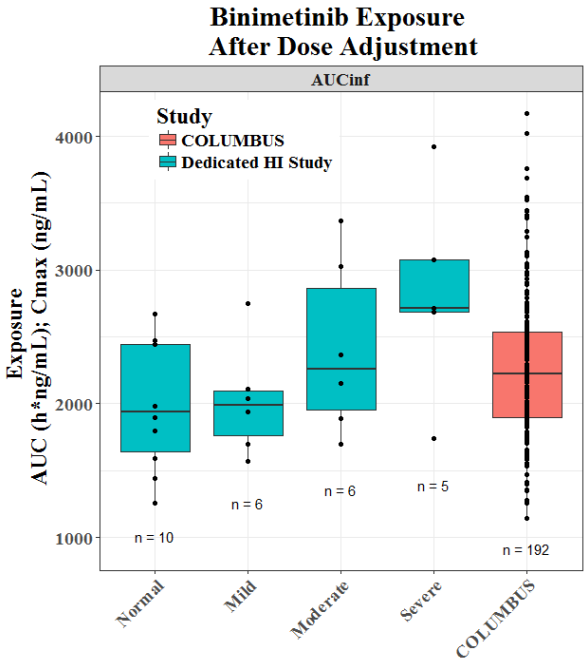


Figure 5. Probability of Retinal Events (Any Grade, Left), CK Increase (Grade 3/4, Middle), and LVEF Decrease (Grade 2+, Right) vs. Binimetinib Exposure Adjusted by Dose Intensity.



Source: NDA (b) (4) cp16-001-addendum2, Figure 4-2, 4-3, 4-4.

Figure 6. Simulation of Exposure after dose adjustment in moderate and severe hepatic impairment based on linear conversion



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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 12 lists the clinical trials included in the NDA submission. The primary evidence to support the clinical of efficacy of encorafenib and binimetinib when given together in patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma is from the randomized clinical trial CMEK162B2301 (hereafter referred to as COLUMBUS). In addition, Array submitted data from 158 patients with advanced unresectable or metastatic BRAF V600-mutated melanoma from trial CLGC818X2109 (hereafter referred to as LOGIC2) to support the efficacy of the combination.

The primary safety data used to characterize the safety profiles of encorafenib and binimetinib when given together is derived from 192 patients treated with encorafenib 450 mg by mouth daily given with binimetinib 45 mg by mouth twice daily (hereafter referred to as Combo 450) treated on COLUMBUS Part 1. The safety experience is supported by safety data from 158 patients with locally advanced or metastatic BRAF V600 mutation-positive melanoma treated with Combo 450 on LOGIC2, 83 patients with BRAF V600 mutation-positive melanoma who received Combo 450 on Trial CMEK162X2110, and 257 patients with BRAF V600 mutation-positive melanoma who received encorafenib 300 mg by mouth once daily and binimetinib 45 mg by mouth twice daily (hereafter referred to as Combo 300) treated on COLUMBUS Part 2. Single-agent safety data for encorafenib and binimetinib was also considered.

Table 12: Clinical Trials Included in the NDA Submission

Trial	Design	Regimen/ schedule/ route	Study Efficacy Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Randomized Trial of Efficacy and Safety						
CMEK162B2391 (COLUMBUS) Part 1	Phase 3, 2-part, randomized, open-label, multi-center, active control	Combo 450: binimetinib 45 mg BID + encorafenib 450 mg QD per 21 day cycle encorafenib 300 mg QD per 21 day cycle vemurafenib 960 mg BID per 21 day cycle	<u>Primary:</u> PFS of Combo 450 vs. vemurafenib <u>Key Secondary:</u> PFS of Combo 450 vs. encorafenib 300 <u>Other Secondary:</u> ORR, TTR, DOR, DCR, QoL, OS	192 194 191	Advanced unresectable or metastatic BRAF V600E or V600K mutation-positive melanoma	162 clinical sites in 28 countries
Part 2		Combo 300: binimetinib 45 mg BID + encorafenib 300 mg QD per 21 day cycle encorafenib 300 mg QD per 21 day cycle	<u>Key Secondary:</u> PFS of Combo 300 vs. encorafenib 300 (Parts 1+ <u>Other Secondary:</u> ORR, TTR, DOR, DCR, QoL, OS	258 86		
Non-randomized Trial to Support Efficacy and Safety						
CLGX818X2109 (LOGIC2) Part 1	Multicenter, nonrandomized, 2-part study of sequential encorafenib/binimetinib combination followed by a rational combination with targeted agents after progression to overcome resistance	Combo 450: binimetinib 45 mg BID + encorafenib 450 mg QD per 21 day cycle	<u>Primary:</u> ORR <u>Other Secondary:</u> PFS, DOR, TTR, DCR	75: BRAF/MEK naïve[1] 83: non-naïve	Locally advanced or metastatic BRAF V600 melanoma	16 clinical sites in 9 countries

Trial	Design	Regimen/ schedule/ route	Study Efficacy Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Non-randomized trials to support safety						
CMEK162X2110	Phase 1b/2, multicenter, open-label, dose-escalation	Phase 1: binimetinib 45 mg BID + encorafenib at the following dose levels: 50 mg QD 100 mg QD 200 mg QD 400 mg QD 450 mg QD 600 mg QD 800 mg QD Phase 2: binimetinib 45 mg BID + encorafenib 450 mg QD	<u>Primary:</u> ORR, DCR (Phase 2 only) <u>Secondary:</u> Phase 1: ORR Phase 2: DOR, TTR, OS	binimetinib 45 mg BID + encorafenib 400 mg QD: 4 450 mg QD: 21 600 mg QD: 62	BRAF dependent advanced solid tumors	
Single-agent encorafenib trials included in the encorafenib pooled safety analysis						
CMEK162B2301 Part 1	Phase 3, 2-part, randomized, open-label, multi-center, active control	encorafenib 300 mg QD	N/A	192	Advanced unresectable or metastatic BRAF V600K mutation-positive melanoma	
CLG818X2101	A Phase 1, multicenter, open-label, dose escalation study of oral encorafenib	encorafenib 300 mg QD	N/A	10	Locally advanced or metastatic BRAF mutation-positive melanoma	
CLGX818X2102	Phase 2, open-label, multicenter, 2-part study with a dose escalation phase with encorafenib alone in BRAF inhibitor naïve	encorafenib 300 mg QD	N/A	15	Locally advanced or metastatic BRAF V600 mutation-positive melanoma	

Trial	Design	Regimen/ schedule/ route	Study Efficacy Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
	patients until PD, followed by a second phase with encorafenib in combination with targeted agents based on tumor biopsy analysis					
Single-agent binimetinib trials included in the binimetinib pooled safety analysis						
CMEK162A2301	Randomized, open-label, multicenter Phase 3 study	Binimetinib 45 mg BID	N/A	269	Advanced, unresectable or metastatic NRAS mutation-positive melanoma	
CMEK162X2201	Phase 2 open-label				Advanced, unresectable or metastatic NRAS mutation-positive melanoma	
Source: Summary of Clinical Safety Tables 1-2, 1-2, and 1-3 [1] data only from BRAF/MEK naïve patients used in primary efficacy analysis						

7.2. Review Strategy

The key materials used for the review of efficacy and safety included:

- Review of the current literature on BRAF-mutant melanoma epidemiology and treatment.
- Review of COLUMBUS, including CSR, protocol, protocol amendments, SAP, and SAP amendments.
- Review and assessment of applicant analysis of encorafenib and binimetinib safety and efficacy in the clinical study report.
- Review of datasets submitted as SAS transport files.
- Review of patient narratives of serious adverse events and deaths.
- Review of minutes of key meetings conducted during encorafenib with binimetinib development for melanoma.
- Review and assessment of Module 2 summaries including the Summary of Clinical Efficacy, Summary of Clinical Safety, Integrated Summary of Efficacy, Integrated Summary of Safety, and proposed labeling modifications for encorafenib and for binimetinib.
- Review of Consultation reports of the Office of Scientific Investigations, QT-IRT, and Ophthalmology.
- Formulation of the benefit-risk analysis and recommendations.
- Review and evaluation of proposed labeling.

Data Sources

The electronic submission including Protocols, SAP, CSRs, SAS transport datasets in SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) format, and SAS codes for the NDA submission are located in the following network paths:

NDA 210496 original submission (encorafenib):

\\CDSESUB1\evsprod\NDA210496\210496.enx

NDA 210498 original submission (binimetinib):

\\CDSESUB1\evsprod\NDA210498\210498.enx

Submissions related to the encorafenib and binimetinib used in combination were submitted to NDA 210496 (encorafenib), and a cross reference to NDA210496 was submitted to NDA 210498 (binimetinib). Submissions related to encorafenib as a single agent were submitted to NDA 210496, and submissions related to binimetinib as a single agent were submitted to NDA 201498.

Data and Analysis Quality

The data submitted with this application were in ADaM and SDTM formats. The data were of good quality and the applicant's analyses were reproducible. Requests for additional information from the applicant through the review process were addressed in a timely fashion. The applicant submitted information regarding their quality assurance plan including their site inspections, the use of central laboratory for hematology and serum chemistry labs, and a certificate of audit.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Table 13 lists the studies included in this review of efficacy.

Table 13: Studies Reviewed for Efficacy

Study	Design	Treatment Regimens Included in Review	Number of Patients Included in Review	Patient Population
COLUMBUS (Part 1)	Phase 3, 2-part randomized, open label, multicenter study	Per 28-day cycle: encorafenib 450 mg QD plus binimetinib 45 mg BID Encorafenib 300 mg QD Vemurafenib 960 mg BID	Part 1 (577 total randomized): 192: Combo 450 194: encorafenib 191: vemurafenib	Patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation
COLUMBUS (Part 2)	Phase 3, 2-part randomized, open label, multicenter study	Per 28-day cycle: encorafenib 300 mg QD plus binimetinib 45 mg BID Encorafenib 300 mg QD	Part 2: (344 patients randomized): 258: Combo 300 86: encorafenib	Patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation
LOGIC2 (Part 1)	Multicenter, nonrandomized, 2-part study	Per 21-day cycle: encorafenib 300 mg QD binimetinib 45 mg BID	Part 1 (158 total): 75: BRAF-inhibitor naïve 83: BRAF-inhibitor non-naïve	Patients with BRAF-mutant locally advanced unresectable or metastatic BRAF V600 melanoma

Source: Adapted from Tabular Listing of Clinical Studies.

8.1.1. COLUMBUS – Trial Design

Overview

Trial CMEK162B2301 (COLUMBUS, Protocol Version 4) was titled **CO**mbined **L**GCX818 **U**sed with **M**EK162 in **B**RAF mutant **U**nresectable **S**kin Cancer, A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib versus LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma (Table 14).

Table 14: COLUMBUS Key Trial Dates

	Part 1	Part 2
First patient randomized	30 Dec 2013	19 Mar 2015
Last patient randomized	10 Apr 2015	10 Nov 2015
Data cutoff (original submission)	19 May 2016	09 Nov 2016
Minimum follow-up time	~ 13 months	~ 12 months
Number of patients	577	344
Trial Sites	162 in 28 countries	116 in 24 countries

Source: FDA Analysis

Part 1 was designed to compare encorafenib in combination with binimetinib to encorafenib alone and to vemurafenib alone. Patients were randomized in a 1:1:1 ratio to one of the three treatment arms:

1) Encorafenib 450 mg by mouth daily plus binimetinib 45 mg by mouth twice daily continuously in 28-day cycles (Combo 450 arm)

2) Encorafenib 300 mg by mouth once daily continuously in 28-day cycles (Encorafenib arm)

3) Vemurafenib 960 mg by mouth twice daily continuously in 28-day cycles (Vemurafenib arm)

Part 2 was designed to estimate the contribution of binimetinib to the effect of the combination. As discussed in “Protocol Amendments,” FDA stated in a meeting that the design of Part 1 was insufficient to determine the contribution of binimetinib to the effect of the combination because the combination arm uses a higher dose of encorafenib (450 mg) than the encorafenib arm alone (300 mg).

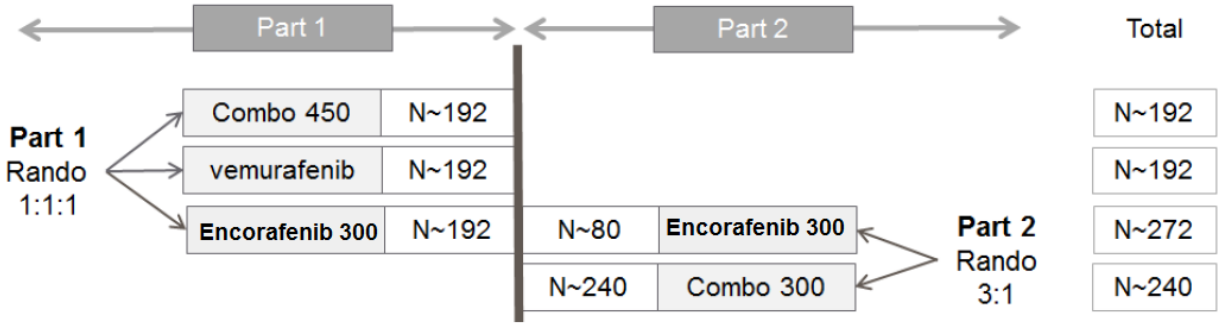
Part 2: Patients were randomized in a 3:1 ratio to one of the two treatment arms:

1) Encorafenib 300 mg by mouth once daily plus binimetinib 45 mg by mouth twice daily continuously in 28-day cycles (Combo 300 arm)

2) Encorafenib 300 mg by mouth once daily continuously in 28-day cycles (Encorafenib arm)

Figure 7 shows the study schema of COLUMBUS, with planned sample sizes.

Figure 7: Study Schema of COLUMBUS



Source: Adapted from Figure 1 of the CSR for Part 1 of COLUMBUS, dated 24-Feb-2017

Randomization was stratified by American Joint Committee on Cancer (AJCC) stage (IIIB + IIIC + VM1a + IV1b vs. IVM1c), ECOG performance status (0 vs. 1), and prior first line immunotherapy (yes vs. no).

Treatment continued until progression, unacceptable toxicity, withdrawal of consent to continue study treatment, death, physician decision or early termination of the study.

All response endpoints were evaluated according to blinded independent review committee (BIRC) central review per RECIST v1.1.

Reviewer's comment: The study was not designed to compare the efficacy or safety of Combo 450 vs. Combo 300.

Study Endpoints

Study objectives and related endpoints are described in Table 15.

Table 15: COLUMBUS Study Objectives and Endpoints

Objective	Endpoint
Primary	
Part 1: To determine whether treatment with Combo 450 prolongs progression free survival (PFS) compared with vemurafenib in patients with BRAF V600 mutant locally advanced unresectable or metastatic melanoma	PFS, defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever occurs first. PFS will be determined based on tumor assessment (RECIST version 1.1 criteria) as per BIRC and survival information.
Key secondary	
Part 1	
To determine the contribution of binimetinib to the regimen of binimetinib plus encorafenib using the PFS comparison Combo 450 vs. LGX818PFS per BIRC as above	PFS per BIRC (as above)

Part 2	
To further quantify the contribution of binimetinib to the regimen of binimetinib plus encorafenib using PFS comparison of Combo 300 vs. LGX818	PFS per BIRC (as above)
Other Secondary	
Part 1 only:	
To compare the treatment effect of Combo 450 vs. vemurafenib in terms of overall survival (OS)	OS, calculated as the time from the date of randomization to date of death due to any cause.
To estimate the treatment effect of Combo 450 vs. LGX818 in terms of overall survival (OS)	OS (as above)
To determine the safety and tolerability of Combo 450 and LGX818 in this patient population	Safety: Adverse events and serious adverse events, changes in laboratory values, vital signs, ECGs, MUGAS/echocardiogram and assessment of physical dermatological and ocular examinations graded according to the NCI CTCAE c4.03
Part 2 only	
To estimate the safety and tolerability of Combo 300 vs. LGX818 in this patient population	Safety (as above)
To estimate the safety and tolerability of Combo 300 vs. Combo 450 in this patient population	Safety (as above)
To estimate the treatment effect of Combo 300 vs. LGX818 in terms of overall survival (OS)	OS (as above)
To estimate the treatment effect of Combo 300 vs. vemurafenib in terms of PFS and OS	PFS per BIRC and OS (as above)
To estimate the treatment effect of Combo 300 vs. Combo 450 in terms of PFS and OS	PFS per BIRC and OS (as above)
Part 1 and 2	
To estimate the treatment effect of LGX818 vs. vemurafenib in terms of PFS and OS	PFS per BIRC and OS (as above)
To assess objective response rate (ORR) by treatment arms	ORR, calculated as the proportion of patient with a best overall response of complete response (CR) or partial response (PR). ORR will be calculated for confirmed and unconfirmed responses separately.
To describe the time to objective response (TTR)	TTR, calculated as the time from date of randomization until first documented CR or PR
To assess disease control rate (DCR) by treatment arms	DCR, calculated as the proportion of patient with a best overall response of CR, PR or stable disease (SD)
To evaluate duration of response (DOR)	DOR, calculated as the time from the date of first documented CR or PR to the first documented progression or death due to underlying cancer
To compare the patient-reported outcomes (PRO) between the treatment arms	Time to definitive 10% deterioration in the FACT-M melanoma subscale and global health status score of the EORTC QLQ-C30. Change from baseline in the FACT-M melanoma subscale, EQ-5D-5L, and global health status score of the EORTC QLQ-C30. Change from baseline in the other EORTC QLQ-C30 subscales.
To compare the ECOG PS between the treatment arms	Time to definitive 1 point deterioration in ECOG PS Change from baseline in ECOG PS

To characterize the pharmacokinetics of LGX818 and MEK162 in this patient population	Plasma concentration-profiles of LGX818 and MEK162 and model based PK parameters

Source: Protocol No. CMEK162B2301 Version 04 Table 3-1 dated 13-Jul-2015.

Endpoints Included in Review

FDA's review of efficacy is limited to analysis of PFS, OS, ORR, and duration of response. The clinical data cutoff date for the final PFS analysis in Part 1 of COLUMBUS was May 19, 2016. The clinical data cutoff date for the final PFS analysis in Part 2 of COLUMBUS was November 9, 2016.

Eligibility Criteria

Key inclusion criteria for COLUMBUS (excerpted from Protocol CMEK162B2301 Version 04) were:

- Age ≥ 18 years
- Histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma or unknown primary melanoma AJCC Stage IIIB, IIIC or IV;
- Presence of BRAF V600E and/or V600K mutation in tumor tissue prior to enrollment, as determined by a designated central laboratory;
- Naive untreated patients or patients who have progressed on or after prior first-line immunotherapy for unresectable locally advanced or metastatic melanoma; Note: Prior adjuvant therapy is permitted (e.g. IFN, IL-2 therapy, any other immunotherapy, radiotherapy or chemotherapy), except the administration of BRAF or MEK inhibitors.
- Evidence of at least one measurable lesion as detected by radiological or photographic methods according to guidelines based on RECIST version 1.1; **Note:** A previously irradiated lesion is eligible to be considered as a measurable lesion provided that there is objective evidence of progression of the lesion since discontinuation of therapy and prior to starting study drug.
- ECOG performance status of 0 or 1;
- Adequate bone marrow, organ function and laboratory parameters:
  - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L,
  - Hemoglobin (Hgb) ≥ 9 g/dL without transfusions,
  - Platelets (PLT)≥_ 100 x 109/L without transfusions,
  - AST and/or ALT ≤ 2.5 × upper limit of normal (ULN); patient with liver metastases ≤ 5 ×ULN,
  - Total bilirubin ≤ 2 × ULN,

- Creatinine ≤ 1.5 mg/dL, or calculated creatinine clearance (determined as per Cockcroft-Gault) ≥ 50mL/min;

- Adequate cardiac function:

- left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram,

- triplicate average baseline QTc interval ≤ 480 ms;

Key Exclusion criteria for COLUMBUS are:

- Any untreated central nervous system (CNS) lesion. However, patients are eligible if: a) all known CNS lesions have been treated with radiotherapy or surgery, b) patient remained without evidence of CNS disease progression ≥ 4 weeks and c) patients must be off corticosteroid therapy for ≥ 3 weeks;
- Uveal and mucosal melanoma;
- History of leptomeningeal metastases;
- History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes);
- History of allogeneic bone marrow transplantation or organ transplantation;
- History of Gilbert's syndrome;
- Previous or concurrent malignancy with the following exceptions:
  - adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing is required prior to study entry),
  - in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to the study,
  - or other solid tumor treated curatively, and without evidence of recurrence for at least 3 years prior to study entry; (note: based on mechanism of action, BRAF inhibitors may cause progression of cancers associated with RAS mutations. Thus, benefits and risks should be carefully considered before administering a BRAF inhibitor to patients with a prior cancer associated with RAS mutation).
- Prior therapy with a BRAF inhibitor (including but not limited to vemurafenib, dabrafenib, LGX818, and XL281/BMS-908662) and/or a MEK inhibitor (including but not limited to trametinib, AZD6244, MEK162, GDC-0973 and RDEA119);
- Any previous systemic chemotherapy treatment, extensive radiotherapy or investigational agent other than immunotherapy, or patients who have received more than one line of immunotherapy for locally advanced unresectable or metastatic melanoma; **Note:** Ipilimumab or other immunotherapy treatment must have ended at

least 6 weeks prior to randomization. Chemotherapy given as part of isolated limb perfusion, regional or intralesional treatment will not be considered systemic treatment;

- Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
  - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) <6 months prior to screening,
  - Symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality <6 months prior to screening except atrial fibrillation and paroxysmal supraventricular tachycardia;
- Uncontrolled arterial hypertension despite medical treatment;
- Patients who have neuromuscular disorders that are associated with elevated CPK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

Dose Modification and Management Guidelines

Dose reduction was allowed for patients who did not tolerate encorafenib or binimetinib. Table 16 shows the dose reduction levels for encorafenib for patients on the Combo 450 arm, the Combo 300 arm, and the encorafenib monotherapy arm. A dose reduction for encorafenib below 50 mg QD was not allowed. Table 17 shows the levels for dose reductions for binimetinib for patients on the Combo 450 arm. A dose reduction for binimetinib below 15 mg BID was not allowed. Dose reductions for a drug were to be based on the highest AE grade.

Table 16: Dose Reductions for Encorafenib

Dose Level	Combo 450 Arm	Combo 300 or Encorafenib Monotherapy Arm
0 (starting dose)	300 mg QD	450 mg QD
-1	200 mg QD	300 mg QD
-2	100 mg QD	200 mg QD
-3	50 mg QD	100 mg QD
-4	Not Allowed	50 mg QD

Source: Columbus Protocol Version 4 Table 6-7, dated 13-Jul-2015

Table 17: Dose Reductions for Binimetinib

Dose Level	Combo 450 or Combo 300 Arm
0 (starting dose)	45 mg BID
-1	30 mg BID
-2	15 mg BID

Source: Columbus Protocol Version 4 Table 6-8, dated 13-Jul-2015

Detailed guidelines for dose adjustments, including interruption, reduction, and permanent discontinuation for encorafenib and binimetinib were specified in the protocol for the following toxicities: the eye disorders of retinal event (including retinal detachment)and/or posterior uveitis, retinal vein occlusion, other eye disorders, liver toxicity based on AST/AST and bilirubin laboratory values, left ventricular systolic dysfunction based on measured LVEF (dose adjustment for binimetinib only), QTcF prolongation, CPK elevation, rash, hand foot skin reaction (dose adjustment for encorafenib only), squamous cell carcinoma/ keratoacanthoma / other suspicion skin lesion (dose adjustment for encorafenib only), diarrhea, nausea/vomiting, and other adverse events suspected to be related to study drug(s).

If a patient on a combination arm discontinued treatment with binimetinib, the patient was allowed to continue treatment with encorafenib; however, because of the limited efficacy of binimetinib monotherapy in the study population, if a patient on a combination arm discontinued treatment with encorafenib, they were also required to discontinue treatment with binimetinib.

For both encorafenib and binimetinib, when the toxicity that resulted in a dose reduction improves to ≤ Grade 1, the dose could be re-escalated at the investigator's discretion provided there were no other concomitant toxicities. The following exceptions applied: binimetinib reduced due to left ventricular dysfunction or prolonged QTc, or encorafenib reduced for prolonged QTc.

Statistical Analysis Plan

The stratified log-rank test was used for PFS and OS endpoints in all analyses, with an overall significance level of 5% (two-sided). The Kaplan-Meier method was used to estimate the PFS and OS curves for each treatment arm, and the Cox proportional hazards model was used for the estimation of hazard ratios for comparisons between arms. Overall type I error was controlled among these endpoints by a hierarchical testing procedure, where the order of testing was

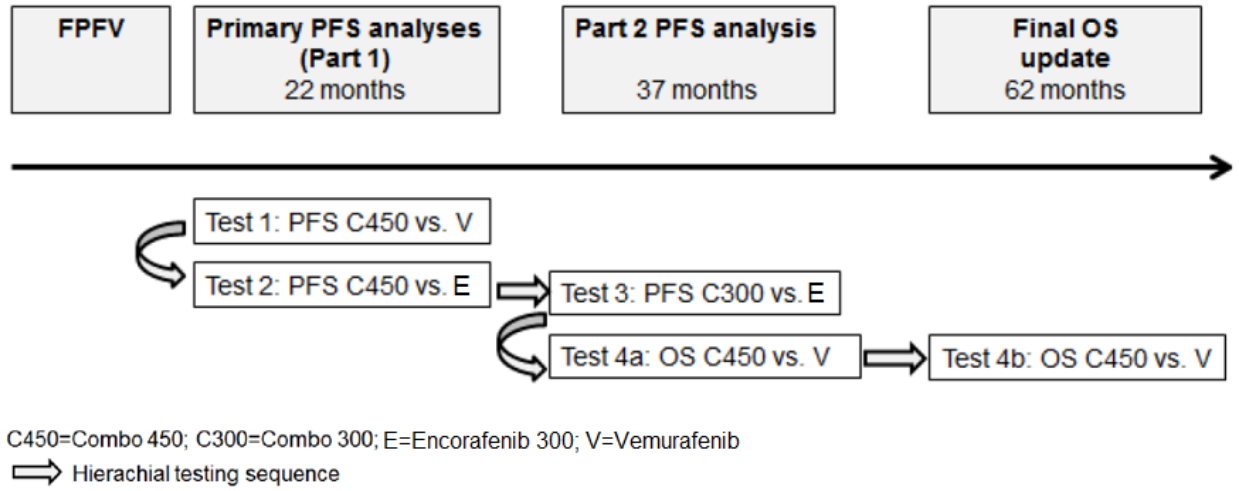
- Test 1: PFS (Combo 450 vs. vemurafenib)
- Test 2: PFS (Combo 450 vs. encorafenib)
- Test 3: PFS (Combo 300 vs. encorafenib)
- Test 4: OS (Combo 450 vs. vemurafenib).

Tests that included the Combo 450 arm were performed on the ITT population from Part 1. In the comparison of the Combo 300 arm and the encorafenib arm (Test 3), the log-rank test was performed using a pooled population for the encorafenib arm, in which all patients randomized to encorafenib monotherapy in either Part 1 or Part 2 were combined, and the ITT population from Part 2 for the Combo 300 arm.

All analyses were event driven, and the estimated times at which they were to take place relative to the first patient's first visit (FPFV) are shown in Figure 8 below. The primary analysis of PFS was planned to occur when Part 1 enrollment completed, and a sufficient number of PFS

events for both the primary and key secondary comparisons were available. This was expected to occur around 22 months after first treatment of the first patient.

Figure 8: Timing of Testing of Primary and Key Secondary Endpoints



Source: Adapted from Figure 2 of the CSR for Part 1 of COLUMBUS, dated 24-Feb-2017

The sample size for Part 1 of this study was estimated using the assumption that the median PFS was 7 months for the vemurafenib arm and 8 months for the encorafenib arm. A total of 577 patients (using a 1:1:1 randomization) were randomized. The study was designed to detect an improvement in median PFS from 8 months in the encorafenib arm to 12 months in the Combo 450 arm. This improvement corresponds to a hazard ratio of 0.667 with 80% power while maintaining an overall significance level of 5% (two-sided). This sample size also provided 90% power to detect a hazard ratio 0.58 for the Combo 450 vs. vemurafenib comparison while maintaining the overall significance level. The study utilized a staggered 25-month enrollment period (8% of total enrollment in months 1 to 7, 22% in months 8 to 14, and 70% in months 15 to 25), a 7-month follow-up period after the last subject is enrolled, and a 10% drop-out rate, yielding a 32-month study.

The sample size for Part 2 of this study was estimated using the assumption that the median PFS was 8 months for the encorafenib arm. A total of 344 patients (using a 3:1 randomization) were randomized in Part 2. Combining the patients randomized to encorafenib in part 1 (194) with those randomized in Part 2, a total of 538 patients were included in the analysis of Test 3. The study was designed to detect an improvement in median PFS from 8 months in the encorafenib arm to 11 months in the Combo 300 arm. This improvement corresponds to a hazard ratio of 0.667 with 80% power while maintaining an overall significance level of 5% (two-sided). Based on accrual assumptions, this was anticipated to occur approximatively 37 months after first treatment of the first patient.

The trial was also designed to test OS, using the assumption that the median OS would be 17 months in the vemurafenib arm and 22 months in the Combo 450 arm. One interim analysis

was planned for OS after 75% of deaths had occurred. The power and alpha spent at each expected analysis time are shown in Table 18. Overall type I error was controlled for the interim analysis with the α-spending function using a Gamma function with parameter 1. This spending function had an alpha allocation of 0.042 to the interim analysis and 0.008 to the final analysis.

Table 18: Expected Number of OS Events and Cumulative Power at Expected Analysis Time Points

Combo 450 versus vemurafenib	Cumulative number of OS events	Boundary to reject H0	Conditional cumulative power to reject H0 (%)*	Cumulative α spent
Part 2 PFS analysis (~37 months)	232	0.7654	46.53	0.021
OS update (~62 months)	309	0.7729	56.64	0.025

*Obtained via EAST5.4 simulations under H1.

Source: COLUMBUS SAP v4 Table 3-1, dated 28-Mar-2017

Reviewer's comment: The power for the OS analysis is low relative to the power for the PFS analyses.

Protocol Amendments

As of the cutoff date for the clinical study report, the original protocol dated 13-May-2013 was amended four times. Table 19 summarizes the major protocol revision for COLUMBUS.

Table 19: Summary of Major Protocol Amendments: COLUMBUS

Version	Version Date	Major Changes
1	03-Oct-2013	• Eligibility criteria changed to allow patients with brain metastases to enroll if they have received standard local treatment with surgery and/or radiotherapy and remain progression free for at least 4 weeks. • Frequency of ophthalmic examinations increased; required Day 1 of every cycle for patients receiving binimetinib and patients in the encorafenib and vemurafenib arms with baseline retinal abnormalities. • Eligibility criteria clarified to allow patients with BRAF V600E and V600K mutations to enroll.
2	20-Dec-2013	• Eligibility criteria changed to allow enrollment of patients who have progressed on or after a first-line immunotherapy. • Stratification factors for randomization amended to add prior first-line immunotherapy (yes versus no) and to remove the stratification for BRAF mutation status (V600E vs. V600K). • Prior first-line immunotherapy (yes versus no) added as a stratification factor for primary analyses.

Version	Version Date	Major Changes
		• Frequency of routine ophthalmic examinations for patients on encorafenib monotherapy and vemurafenib arms without baseline retinal abnormalities changed to screening, cycle 4, Day 1, every 12 weeks thereafter, end of therapy (EOT), and 30-day post EOT. In addition, dose modification guidelines for eye disorders were updated. These changes were based on preclinical data.
3	04-Nov-2014	• The study was amended to add part 2, addressing a request from the FDA to compare 300mg QD LGX818 plus 45mg BID MEK162 with the LGX818 monotherapy arm. • Testing strategy in Part 1 modified to a hierarchical testing of PFS for Combo 450 vs. vemurafenib (primary endpoint) and Combo 450 vs. encorafenib 300 monotherapy. The analysis of encorafenib 300 monotherapy vs. vemurafenib was changed to a secondary endpoint. • Due to the expected low size for the prior immunotherapy "yes" strata, both prior immunotherapy strata (yes and no) were combined and the analysis was stratified by cancer stage and ECOG PS. • Eligibility criteria amended to allow enrollment of patients with melanoma of unknown primary origin. • Renal failure, hemorrhage, and thrombotic events added to the list of notable AEs for encorafenib and/or encorafenib with binimetinib based on new safety information.
4	13-Jul-2015	• Documented a change in study sponsorship from Novartis to Array BioPharma • Study design and procedures not affected

Source: COLUMBUS Part 1 Protocol and Protocol amendments submitted to Application 30-Jun-2017.

Protocol v2 added prior first-line immunotherapy (yes vs. no) as a stratification factor for randomization, and removed BRAF mutation status (V600E vs. V600K) as a stratification factor for randomization. BRAF mutation status was not specified as a stratification factor in the primary analyses. As stated in protocol v0:

> *"Due to the relatively low expected prevalence of V600K mutation (around 10 - 15%), the two types of mutations will be combined at the time of the analysis to avoid small or empty strata. The log-rank test will therefore be stratified by the two randomization strata variables cancer stage and ECOG PS."*

When prior first-line immunotherapy was added as stratification factor for randomization in protocol v2, it was also added as a stratification factor for the primary analyses. In protocol v3, this stratification factor for the primary analyses was removed. As stated in protocol v3:

> *"Due to the relatively low expected prevalence of patients with prior immunotherapy (around 15%), the two prior immunotherapy strata (yes and no) will be combined at the time of the analysis to avoid small or empty strata. The log-rank test will therefore be stratified by the two randomization strata variables cancer stage and ECOG PS."*

On April 28, 2014, FDA communicated the following concern to the Applicant about the design of the trial:

> *"…comparing encorafenib plus binimetinib to encorafenib alone will also not allow FDA to determine the contribution of binimetinib to the combination because the combination arm uses a higher dose of encorafenib (450 mg) than the encorafenib alone arm (300 mg)…the encorafenib alone arm should use the same or higher dose than the dose of encorafenib as used in the combination arm. Otherwise, the contribution of binimetinib to the effect of the combination therapy may not interpretable."*

Protocol v3 added a second part (Part 2) to COLUMBUS, with the intention of isolating the effect of binimetinib in the combination. The proposed test to address this isolation was a test which pooled patient data from Parts 1 & 2 in an encorafenib group, which was to be compared to patients randomized in Part 2 to Combo 300. A review of protocol v3 yielded the following comment from FDA which was conveyed to the sponsor on February 18, 2015:

"In general, we have no objections to the revised study design and the statistical analysis plan (Protocol CMEK162B2301, Version 03) which is intended to assess the contribution of binimetinib to the effect of the combination. We note, however, that patients may be randomized to the single-agent encorafenib arm at a dose of 300 mg daily in both Part 1 and Part 2, whereas patients may be randomized to the low-dose combination (encorafenib 300 mg plus binimetinib) arm in Part 2 only. Since there are separate randomizations for Parts 1 and 2, there may be some imbalance in important patient characteristics with potential introduction of bias in the analyses of these data. Therefore, the interpretation of analyses comparing the low-dose combination arm (encorafenib 300 mg), which is limited to patients enrolled in Part 2 of the trial to the single-agent encorafenib arm, which includes patients enrolled in Parts 1 and 2 of the trial, will depend, in part, on the results of the trial. The adequacy of the revised study design and statistical analysis plan to demonstrate the contribution of binimetinib to the effect of the combination, as supported by the data, should be discussed in a pre-NDA meeting, and will be a review issue."

8.1.2. LOGIC2 – Trial Design

Overview

LOGIC2 was a two-part, multicenter, multi-cohort, non-comparative, open-label study in patients with BRAF mutant locally advanced unresectable or metastatic melanoma. Three populations of patients were eligible for participation in Part 1:

- Group A: Patients naïve to treatment with BRAF inhibitors.
- Group B: Patients who had progressed after single-agent BRAF or MEK inhibitors; patients who had progressed after receiving a BRAF inhibitor in combination with a MEK inhibitor (other than encorafenib/binimetinib); patients who were receiving encorafenib and/or binimetinib who had not yet progressed; or, in consultation with the Sponsor,

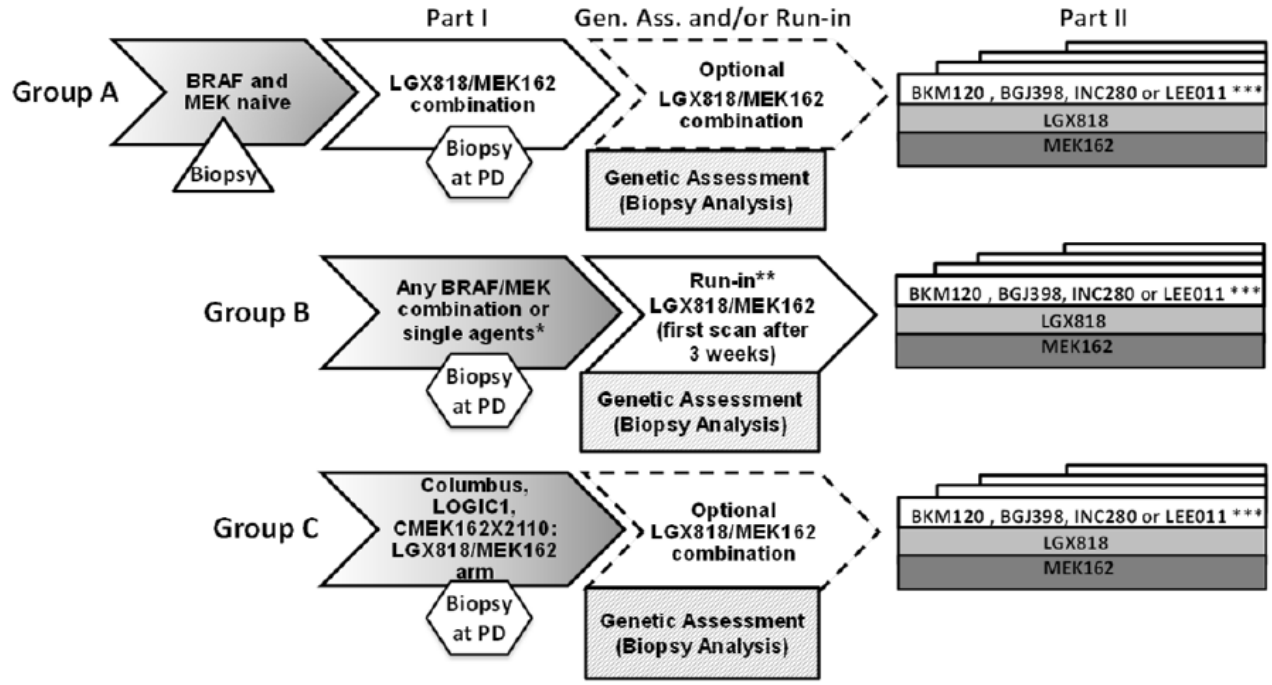
patients who had received any BRAF and/or MEK inhibitor other than encorafenib and/or binimetinib who had not yet progressed.

- Group C: Patients who progressed after encorafenib/binimetinib combination therapy.

In Part 1, 75 patients naïve to selective BRAF and MEK inhibitors (Group A) were treated with the encorafenib/binimetinib combination at the RP2D of 450 mg once daily (QD) and 45 mg twice daily (BID) until disease progression (as defined per RECIST v1.1).

Based on the genetic assessment of a tumor biopsy obtained at disease progression, patients who relapsed after encorafenib/binimetinib combination therapy could enter Part 2 of the study for tailored combination treatment in 1 of 4 arms. Figure 9 shows the study design.

Figure 9: Study Design for Study LOGIC2



*Single agents: i.e. Vemurafenib, Dabrafenib, LGX818, Trametinib, MEK162; Combos: i.e. Dabrafenib/Trametinib, LGX818/MEK162 combination

**Patients who progressed on a previous BRAFi and/or MEKi regimen will continue on LGX818/MEK162 if PR is observed, followed by new Biopsy at progression. Patients who did not progress on their prior BRAFi/MEKi regimen may continue LGX818/MEK162 combination until evidence of disease progression at which point a tumor biopsy will be taken and analyzed to guide assignment to a triple combination arm in Part II.

***LEE011 cohort might start directly at the RP2D established in CMEK162X2110, if available.

Note: As of 10 July 2015, the triple combination of LGX818/MEK162 + BKM120 is no longer being explored.

Source: LOGIC2 CSR Figure 1, dated 31-Jul-2014.

Study Endpoints

The primary objective of LOGIC2 was to assess the anti-tumor activity of encorafenib + binimetinib in combination with a third targeted agent after progression on encorafenib + binimetinib combination therapy in Part 2. A primary efficacy endpoint for Part 1 was not defined in the study protocol. The primary efficacy endpoint for Part 2 of the study was ORR as determined by Investigator-assessed tumor evaluations per RECIST v1.1. Array performed an evaluation of this endpoint for Part 1 of the study, which is presented in this review.

PFS as determined by investigator was listed as a secondary endpoint.

Statistical Analysis Plan

ORR was provided with a corresponding 95% confidence interval (CI) based on Clopper and Pearson's method for all patients. The sample size was estimated based on power calculations for Part 2 of this study. It was expected that approximately 140 patients would enroll in Part 2 of the study to address the primary objective of the study. Descriptive statistics using Kaplan-Meier methods were provided for PFS.

8.1.3. COLUMBUS – Study Results

Compliance with Good Clinical Practices

The applicant stated that the clinical trial protocol, informed consent form (ICF), and printed patient information materials were reviewed and approved by the independent ethics committee (IEC) and/or institutional review boards (IRB) for each site before any study procedures were performed. Any subsequent protocol amendments or informed consent revisions were approved by the IRB or IEC before any changes were initiated.

According to the applicant, the study was conducted according to International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines concerning Good Clinical Practice (GCP), the European Union Clinical Trials Directive (2001/20/EC), Title 21 of the US Code of Federal Regulations (21 CFR) and the practices and regulations of each participating nation. Written informed consent to participate in the study was obtained from each patient before any study-specific procedures were performed.

Financial Disclosure

Novartis Pharmaceuticals Corporation transferred to Array Biopharma Inc. all development and commercial rights to binimetinib and encorafenib under a set of asset transfer and related agreements in March 2015. Financial disclosure information was obtained for interest in both Novartis and Array.

At the Pre-NDA meeting of 06 February 2017, the Applicant agreed to submit financial information for the following clinical trials:

- CMEK162B2301 (COLUMBUS)
- CLGX818X2109 (LOGIC2)
- CLGX818X2101

In accordance with 21 CFR 54.2, the applicant submitted a list investigators for these trials attached to FDA form 3454 certifying that the Principal Investigators and Sub-investigators had no financial information to disclose as defined in 21 CFR 54.2(a, b, and f) that could affect the outcome of the study. The Applicant states all information submitted was current as of end of March 2017. John R. Moore, Vice President and General Counsel, Array BioPharma Inc, certified this disclosure information for the applicant.

Financial disclosure information was missing for some investigators. By study, the percentage of investigators for which disclosure was missing is as follows: CMEK162B2301 (COLUMBUS): 3%, CLGX818X2109 (LOGIC2): 2%, CLGX818X2101: 4%. No reporting investigators had disclosable financial interests and/or arrangements.

This reviewer concludes the impact of potential bias due to the missing financial disclosure information is minimized by the small number of patients treated at any single site compared to the total number of patients treated in each trial.

Data Quality and Integrity

Data, statistical programs, and study reports of this application were submitted electronically. The overall quality of the submission is acceptable, and the reviewer was able to perform all analyses using the submitted data. Derivations for key variables were verified, as well as demographic variables. No inconsistencies were found in the reported efficacy results or patient baseline characteristics.

Patient Disposition

Table 20 summarizes the disposition of patients in Part 1 of COLUMBUS. A higher percentage (53%) of patients discontinued treatment due to progression on the vemurafenib arm than on the Combo 450 and encorafenib arms (43% and 45%, respectively). The Combo 450 arm had the highest percentage (35%) of patients with treatment ongoing at the time of data cutoff, followed by encorafenib (24%) and vemurafenib (14%).

Table 20: Patient Disposition in Part 1 of COLUMBUS

	Combo 450 N=192 n (%)	Encorafenib (Part 1) N=194 n (%)	Vemurafenib N=191 n (%)
Treatment received (%)			
YES	192 (100)	192 (99)	186 (97)
NO	0 (0)	2 (1)	5 (3)
Primary reason for treatment discontinuation (%)			
ADVERSE EVENT	16 (8)	24 (12)	26 (14)
DEATH	7 (4)	1 (1)	4 (2)
LOST TO FOLLOW-UP	1 (1)	1 (1)	0 (0)
PHYSICIAN DECISION	8 (4)	19 (10)	13 (7)
PROGRESSIVE DISEASE	83 (43)	87 (45)	101 (53)
PROTOCOL DEVIATION	2 (1)	1 (1)	0 (0)
SUBJECT/GUARDIAN DECISION	7 (4)	13 (7)	15 (8)
UNTREATED	0 (0)	2 (1)	5 (3)
TREATMENT ONGOING	68 (35)	46 (24)	27 (14)
Treatment ongoing (%)			
YES	68 (35)	46 (24)	27 (14)
NO	124 (65)	146 (75)	159 (83)
UNTREATED	0 (0)	2 (1)	5 (3)

Source: FDA Analysis.

Table 21 summarizes the disposition of patients in Part 2 of COLUMBUS. A higher percentage (45%) of patients discontinued treatment for progressive disease on the encorafenib arm than on the Combo 300 arm (37%). The Combo 300 arm had a higher percentage of patients (39%0 with treatment ongoing at the time of the data cutoff than the encorafenib (Part 2) arm (26%).

Table 21: Patient Disposition in Part 2 of COLUMBUS

	Encorafenib (Part 2) N=86 n (%)	Encorafenib 300mg + Binimetinib N=258 n (%)
Treatment received (%)		
YES	84 (98)	257 (100)
NO	2 (2)	1 (0)
Primary reason for treatment discontinuation (%)		
ADVERSE EVENT	6 (7)	22 (9)
DEATH	1 (1)	8 (3)
LOST TO FOLLOW-UP	1 (1)	0 (0)
PHYSICIAN DECISION	8 (9)	22 (9)
PROGRESSIVE DISEASE	39 (45)	96 (37)
PROTOCOL DEVIATION	0 (0)	0 (0)
SUBJECT DECISION	7 (8)	8 (3)
UNTREATED	2 (2)	1 (0)
TREATMENT ONGOING	22 (26)	101 (39)
Treatment ongoing (%)		
YES	22 (26)	101 (39)
NO	62 (72)	156 (60)
UNTREATED	2 (2)	1 (0)

Source: FDA Analysis

Protocol Violations/Deviations

The incidence of patients with at least one protocol deviation was similar among the 3 treatment arms (62% Combo 450, 66% encorafenib monotherapy, 64% vemurafenib). Most protocol deviations were due to key procedures not performed as per protocol (48% Combo 450, 53% encorafenib monotherapy, 55% vemurafenib). Deviations due to eligibility criteria not met were reported for patients in each treatment arm (9% Combo 450, 11% encorafenib, 5% vemurafenib). Table 22 summarizes selection criteria protocol deviations by specific criteria not met. Of note, 1% of patients across arms did not meet laboratory parameters indicating adequate organ function. This was more prevalent in the encorafenib monotherapy arm compared to the other arms, but the overall frequency was low for all arms. In addition, 1.2% of patients across arms were enrolled despite having untreated CNS lesion(s). This was balanced between the Combo 450 (2.1%) and encorafenib monotherapy (1.5%) arms; no patients with untreated CNS lesion(s) were enrolled in the vemurafenib monotherapy arm.

Table 22: Summary of Deviations from Eligibility Criteria for COLUMBUS Part 1

	COLUMBUS Part 1			
	Combo 450 N=192 n (%)	Enc 300 N=194 n (%)	Vem N=191 n (%)	Total across arms
Selection criteria not met[1]	**17 (8.9)**	**21 (10.8)**	**10 (5.2)**	**47 (8.1)**
Inadequate bone marrow, organ function and/or laboratory parameters	1 (0.5)	4 (2.1)	1 (0.5)	6 (1.0)
Previous or concurrent malignancy	1 (0.5)	0	0	1 (0.2
Previous treatment for unresectable locally advanced or metastatic melanoma [2 or] other than first line immuno therapy [3]	1 (0.5)	0	1 (0.5)	1 (0.2
Prior therapy with a BRAF and/or MEK inhibitor	0	1 (0.5)	0	1 (0.2)
History of retinal degenerative disease [2]	0	0	1 (0.5)	1 (0.2)
Inadequate cardiac function	0	1 (0.5)	0	1 (0.2)
No adequate pregnancy test at study entry	7 (3.6)	8 (4.1)	5 (2.6)	20 (3.5)
No central confirmation of BRAF V600E and/or V600K mutation	0	2 (1.0)	0	2 (0.3)
No evidence of measurable lesion	1 (0.5)	0	1 (0.5)	2 (0.3)
No histologically confirmed diagnosis of melanoma[4]	1 (0.5)	1 (0.5)	0	2 (0.3)
Uncontrolled arterial hypertension	3 (1.6)	1 (0.5)	1 (0.5)	5 (0.9)
Untreated CNS lesion	4 (2.1)	3 (1.5)	0	7 (1.2)
Uveal or mucosal melanoma	2 (1.0)	1 (0.5)	0	3 (0.5)

Source: CSR COLUMBUS Part 1 Table 14.1-1.8a submitted to application 30-Jun-2017: Note Reviewer corrected Applicant's table for Previous treatment for unresectable locally advanced or metastatic melanoma or other than first line immuno therapy to include patient in vemurafenib arm who received dacarbazine.

[1] Patients with more than one criteria not met is counted once. A patient, however, may be included in more than one specific selection criteria (row)

[2] Under initial protocol

[3] After Amendment 1

[4] After Amendment 3 (cutaneous melanoma prior to Amendment 3)

All patients who were randomized were evaluated in the full analysis set (FAS). The per protocol set (PPS) comprised all patients from the FAS without a major protocol deviation and who received at least one dose of study. Twenty-one patients (3.6%) overall were excluded from the

per protocol set. The reasons for exclusion are summarized by arm in Table 23 below. The most common reason that patients were excluded from the PPS was failure to receive at least one dose of study medication (0% Combo 450, 1% encorafenib, 3% vemurafenib).

Table 23: Reasons Leading to Exclusion of Patients from Per-protocol Set: Columbus Part 1

Reason	Combo 450 N=192 n (%)	Enc 300 N=194 n (%)	Vem N=191 n (%)
Patient excluded from Per-protocol set	**4 (2.1)**	**10 (5.2)**	**7 (3.7)**
Patient did not receive at least one dose of study medicine	0	2 (1.0)	5 (2.6)
No histologically confirmed diagnosis of unresectable or metastatic cutaneous melanoma or unknown primary melanoma (Stage IIIB, IIIC to IV per AJCC) [1]	1 (0.5)	1 (0.5)	0
Not positive for BRAF V600 mutation [1]	0	2 (1.0)	0
Prior treatment for unresectable or metastatic cutaneous melanoma other than immunotherapy [1]	1 (0.5)	0	0
Prior treatment with a RAF and/or MEK inhibitor [1]	0	1 (0.5)	0
No measurable lesion as detected by local review of radiological or photographic methods based on RECIST version 1.1 [1]	1 (0.5)	0	1 (0.5)
New anti-neoplastic therapy administered after start of treatment and prior to first tumor assessment	1 (0.5)	4 (2.1)	1 (0.5)

Source: CSR COLUMBUS Part 1 Table 15 submitted to application 30-Jun-2017, Reviewer verified.
[1] Major protocol deviation

Additional details regarding patients who were excluded from per-protocol set for reasons other than patient did not receive at least one dose of study medication are summarized as follows:

- No histologically confirmed diagnosis of unresectable or metastatic cutaneous melanoma or unknown primary melanoma (Stage IIIB, IIIV to IV per AJCC)
  - Patient (b) (6) (Combo 450 arm): The patient was noted to have skin melanoma Stage M1C at study entry and a positive BRAF mutation test result that was conducted on melanoma tissue; however, there was no histologically confirmed diagnosis of unresectable or metastatic cutaneous melanoma or unknown primary. The patient was randomized to and treated with Combo 450. The patient was discontinued from treatment on study day 225 due to progressive disease and was evaluated in the FAS.
  - Patient (b) (6) (encorafenib arm): The patient was noted to have skin melanoma Stage IV M1C at study entry and a positive BRAF mutation test result that was conducted on melanoma tissue; however, there was no histologically confirmed

diagnosis of unresectable or metastatic cutaneous melanoma or unknown primary. The patient was randomized to and treated with encorafenib monotherapy. The patient was still receiving study treatment as of the cutoff state and was evaluated in the FAS.

- Not positive for BRAF V600 mutation
  - Patient (b) (6) (encorafenib arm): The central laboratory did not confirm the BRAF mutation-positive status of the patient (indeterminate). It is unknown if the patient had a local BRAF mutation-positive result. The patient was treated with encorafenib and discontinued treatment on study day 208 due to an AE. The patient was evaluated in the FAS.
  - Patient (b) (6) (encorafenib arm): The central laboratory did not confirm the BRAF mutation-positive status of the patient (indeterminant). The patient was randomized based on local BRAF-mutation testing. The patient was treated with encorafenib and discontinued treatment on study day 103 due to physician decision. The patient was evaluated in the FAS.
- Prior treatment for unresectable or metastatic cutaneous melanoma other than immunotherapy:
  - Patient (b) (6) (Combo 450 arm): The patient received prior therapy in the metastatic setting with ipilimumab which was prohibited by the protocol. In addition, the minimum 6-week washout period for prior therapies was not followed. The patient was treated with Combo 450 and discontinued treatment on Study day 154 due to progressive disease. The patient was evaluated in the FAS.
- Prior treatment with a RAF and/or MEK inhibitor
  - Patient (b) (6) (encorafenib arm): The patient received prior therapy with the BRAF inhibitor vemurafenib. The patient was treated with encorafenib and discontinued treatment on Study day 87 due to the protocol deviation. The patient was evaluated in the FAS.
- No measurable lesion as detected by local review of radiological or photographic methods based on RECIST v 1.1
  - Patient (b) (6) (Combo 450): The patient was specified as not having a measurable lesion by local review. The patient had a dermatological lesion that was the target lesions (11 X 10 mm); however, this lesion was removed during the screening phase, prior to randomization. The patient was treated with encorafenib and discontinued treatment on Study day 87 due to the protocol deviation. The patient was evaluated in the FAS.
  - Patient (b) (6) (vemurafenib): The patient was specified as not having a measurable lesion by local review; however, the BIRC review showed subcutaneous non-nodal lesions on CT. The patient was treated with vemurafenib and discontinued from treatment on Study day 311 due to PD. The patient was evaluated in the FAS.

- New anti-neoplastic therapy administered after start of study treatment and prior to first tumor assessment
  - Patient [redacted] (Combo 450): During treatment, the patient received palliative radiotherapy to the bone prior to the first tumor assessment. Because the radiotherapy was not administered due to evidence of progression, it was not considered a reason to discontinue study treatment per protocol. The patient was still receiving study treatment as of the cutoff date. The patient was evaluated in the FAS.
  - Patient [redacted] (encorafenib arm): The patient initiated treatment with encorafenib but discontinued on Study Day 9 due to an adverse event. The patient received subsequent antineoplastic therapy with dabrafenib/trametinib starting on Study Day 15. The patient was evaluated in the FAS.
  - Patient [redacted] (encorafenib): The patient initiated treatment but discontinued on Study Day 1 due to subject/guardian decision with the reason of "swallowing trouble" specified. The patient then received subsequent antineoplastic therapy with vemurafenib starting on Study day 22. The patient was evaluated in the FAS.
  - Patient [redacted] (encorafenib): The patient initiated treatment but discontinued on Study day 15 due to an adverse event. The patient received subsequent antineoplastic therapy with dabrafenib starting on Study day 18. The patient was evaluated in the FAS.
  - Patient [redacted] (encorafenib): The patient initiated treatment but discontinued on Study day 22 due to an adverse event. The patient received subsequent antineoplastic therapy with vemurafenib starting on Study day 34. The patient was evaluated in the FAS.
  - Patient [redacted] (vemurafenib): The patient initiated treatment but discontinued on Study day 8 due to an adverse event. The patient received subsequent antineoplastic therapy with dabrafenib starting on Study Day 26 and then pembrolizumab starting on study day 64. The patient was evaluated in the FAS.

Demographic Characteristics

Part 1 of COLUMBUS was conducted at 162 centers in 28 countries and Part 2 was conducted at 116 clinical sites in 24 countries, with some sites used in both study parts. A total of 921 patients were randomized (Part 1: 577 patients in a 1:1:1 allocation to Combo 450, Encorafenib, and Vemurafenib; Part 2: 344 patients in a 3:1 allocation to Combo 300 and Encorafenib). In Part 1, the Combo 450 arm had the highest percentage of patients aged 65 and older (31%), followed by Vemurafenib (27%), and Encorafenib (21%). The mean age was similar across these arms. Otherwise, the demographics of the patients in Part 1 appear to be balanced as summarized in Table 24. In Part 2, there was a higher percentage of women (49%) in the encorafenib arm than the Combo 300 arm (41%). Otherwise, the demographics appear to be generally balanced over the two arms.

Table 24: Patient Demographics in COLUMBUS

	Part 1			Part 2	
	Combo 450	**Encorafenib**	**Vemurafenib**	**Combo 300**	**Encorafenib**
N	192	194	191	258	86
Age (mean (sd))	56.2 (13.6)	54.6 (12.6)	55.2 (14.2)	57.4 (14.0)	55.8 (14.7)
Age Category (%)					
<65	132 (69)	154 (79)	140 (73)	175 (68)	60 (70)
>=65	60 (31)	40 (21)	51 (27)	83 (32)	26 (30)
Sex (%)					
F	77 (40)	86 (44)	80 (42)	107 (41)	42 (49)
M	115 (60)	108 (56)	111 (58)	151 (59)	44 (51)
Race (%)					
MISSING	1 (1)	1 (1)	1 (1)	0 (0)	1 (1)
AMERICAN INDIAN OR ALASKA NATIVE	0 (0)	2 (1)	2 (1)	0 (0)	0 (0)
ASIAN	5 (3)	6 (3)	8 (4)	15 (6)	7 (8)
BLACK OR AFRICAN AMERICAN	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
OTHER	3 (2)	2 (1)	2 (1)	2 (1)	0 (0)
UNKNOWN	2 (1)	9 (5)	11 (6)	4 (2)	0 (0)
WHITE	181 (94)	174 (90)	167 (87)	236 (91)	78 (91)
ECOG[1] (%)					
0	139 (72)	143 (74)	140 (73)	191 (74)	62 (72)
1	53 (28)	51 (26)	51 (27)	67 (26)	24 (28)

Source: FDA Analysis
[1] One patient from Part 2 who had an ECOG status of 2 has been omitted.

Baseline Disease Characteristics

Table 25 summarizes the baseline disease characteristics of patients randomized on COLUMBUS. Baseline disease characteristics were generally well-balanced across arms within Part 1 and within Part 2.

Table 25: Patient and Disease Characteristics in COLUMBUS

	Part 1			Part 2	
	Combo 450	**Encorafenib**	**Vemurafenib**	**Combo 300**	**Encorafenib**
N	192	194	191	258	86
Primary site of cancer (%)					
SKIN MELANOMA	191 (99)	192 (99)	190 (99)	239 (93)	79 (92)
OTHER	1 (1)	2 (1)	1 (1)	18 (7)	7 (8)
MISSING	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
Stage at time of study entry (%)					
STAGE IIIB	0 (0)	2 (1)	1 (1)	0 (0)	0 (0)
STAGE IIIC	9 (5)	4 (2)	10 (5)	8 (3)	5 (6)
STAGE IV M1A	26 (14)	29 (15)	24 (13)	31 (12)	13 (15)
STAGE IV M1B	34 (18)	39 (20)	31 (16)	47 (18)	10 (12)
STAGE IV M1C WITH ELEVATED LDH	50 (26)	50 (26)	36 (19)	73 (28)	32 (37)
STAGE IV M1C WITH NORMAL LDH	73 (38)	70 (36)	89 (47)	99 (38)	26 (30)
Number of organs involved at baseline (%)					
1	47 (24)	56 (29)	45 (24)	78 (30)	23 (27)
2	58 (30)	52 (27)	59 (31)	66 (26)	22 (26)
3	45 (23)	42 (22)	42 (22)	59 (23)	19 (22)
>3	42 (22)	44 (23)	45 (24)	55 (21)	22 (26)
LDH at baseline (%)					
<=ULN	137 (71)	147 (76)	139 (73)	178 (69)	54 (63)
>ULN	55 (29)	47 (24)	52 (27)	80 (31)	32 (37)

Source: FDA Analysis

Prior Antineoplastic Therapy

Table 26 summarizes the proportion of patients who received prior antineoplastic therapy. The percentage of patients who had received any prior antineoplastic therapies was similar across the three treatment arms. For a specific therapy type, the percentage of patients who received prior systemic treatment or who had prior surgery was similar across arms, but a higher

percentage of patients in the encorafenib monotherapy arm (22%) received prior radiotherapy as compared with either the Combo 450 (16%) or vemurafenib (13%) arms.

Prior to Amendment 2, prior chemotherapy was allowed only in the adjuvant setting or as local-regional treatment. Two patients previously treated with chemotherapy in the metastatic setting were enrolled, one in the Combo 450 arm and one in the vemurafenib arm. Both patients received dacarbazine.

Protocol Amendment 2 permitted enrollment of patients who progressed on or after first-line treatment with immunotherapy for unresectable locally advanced or metastatic melanoma. Eleven patients (1.9%) overall received prior chemotherapy in the adjuvant setting: 3 patients in the Combo 450 arm (1.6%), 4 patients in the encorafenib monotherapy arm (2.1%), and 4 patients in the vemurafenib arm (2.1%).

For any disease setting (adjuvant or advanced/metastatic disease), a similar percentage of patients (30% Combo 450, 30% encorafenib monotherapy, 30% vemurafenib) received prior immunotherapy (based on the eCRF and not IRT stratification data) (Table 27). Prior use of interferons/interleukins was most common. Few patients received prior ipilimumab or anti-PD1/PDL1 inhibitors (0.5% overall).

Table 26: Prior Therapy, Including Immunotherapy (starting amendment 2)

	COLUMBUS Part 1		
	Combo 450 N=192 n (%)	**Encorafenib N=194 n (%)**	**Vemurafenib (N=191) n (%)**
Any Therapy	**158 (82.3)**	**161 (83.0)**	**165 (86.4)**
Medication	62 (32.2)	63 (32.5)	59 (30.9)
Surgery	146 (76.0)	149 (76.8)	157 (82.2)
Radiotherapy	30 (15.6)	42 (21.6)	25 (13.1)
Medication: Setting at last treatment			
Adjuvant	52 (27.1)	46 (23.7)	46 (24.1)
Neoadjuvant	0	1 (0.5)	1 (0.5)
Therapeutic – Metastatic	10 (5.2)	16 (8.2)	12 (6.3)

Source: CSR COLUMBUS Part 1 Table 11 submitted to application June 30, 2017

Table 27: Prior Immunotherapy Any Setting: Columbus Part 1

	COLUMBUS Part 1		
	Combo 450 N=192 n (%)	**Encorafenib N=194 n (%)**	**Vemurafenib (N=191) n (%)**
Any Immunotherapy	**57 (29.7)**	**58 (29.9)**	**57 (29.8)**
Ipilimumab	7 (3.6)	10 (5.2)	7 (3.7)
Anti-PD1/PDL1	1 (0.5)	2 (1.0)	0
Interferons/Interleukins	51 (26.6)	51 (26.3)	52 (27.2)

Source: CSR COLUMBUS Part 1 Table 12 submitted to application June 30, 2017

Efficacy Results – Primary Endpoint

In the analyses that follow, cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1) were specified as stratification factors. As discussed in "Protocol Amendments", protocol v2 added prior first-line immunotherapy (yes vs. no) as a stratification factor for the primary analyses, and protocol v3 subsequently removed this stratification factor for the primary analyses, although it was retained as a stratification factor for randomization.

Table 28 presents the primary analysis of PFS for the Combo 450 arm compared with the vemurafenib arm. The Combo 450 arm demonstrated significant improvement in progression-free survival when compared to the vemurafenib arm, with a stratified log-rank test p-value of <0.0001.

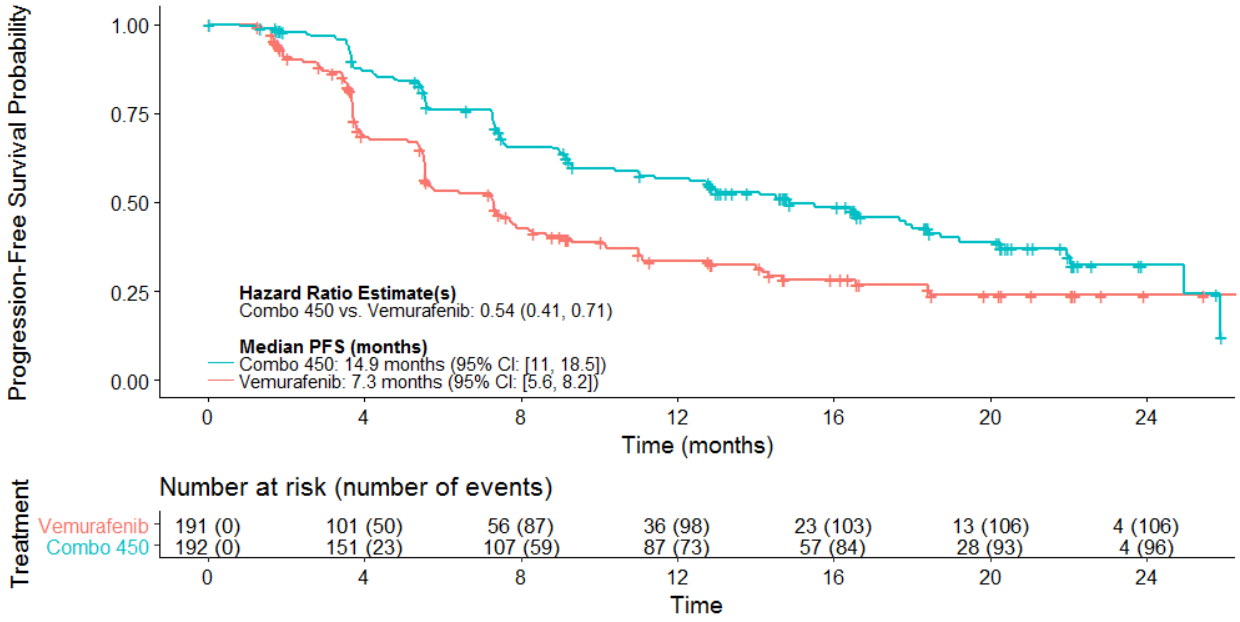
The estimated median PFS times were 14.9 months (95% CI: [11.0, 18.5]) for the Combo 450 arm and 7.3 (95% CI: [5.6, 8.2]) for the vemurafenib arm. The stratified hazard ratio of PFS for the Combo 450 arm compared to the vemurafenib arm was 0.54 (95% CI: [0.41, 0.71]). Figure 10 shows the PFS curves, estimated using the Kaplan-Meier method. The curves diverge around 2 months and retain separation until about 24 months.

Table 28: Progression-Free Survival in the ITT Population for Part 1 of COLUMBUS (Combo 450 vs. Vemurafenib)

	Vemurafenib N = 191	**Combo 450 N = 192**
Number of events (%)	106 (55)	98 (51)
Censored (%)	85 (45)	94 (49)
Median PFS[1] in months (95% CI)	7.3 (5.6, 8.2)	14.9 (11.0, 18.5)
Hazard Ratio (95% CI)[2]	0.54 (0.41, 0.71)	
P-value[3]	<0.0001	

Source: FDA Analysis
[1] BIRC central review
[2] Estimated with the Cox proportional hazards model stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1).
[3] Two-sided p-value estimated with the log-rank test stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1).

Figure 10: Kaplan-Meier Plot of Progression-Free Survival in the ITT Population for Part 1 of COLUMBUS (Combo 450 vs. Vemurafenib)



Source: FDA Analysis

Follow-up time was similar across arms, with a median potential follow-up time for PFS of 14.4 months (95% CI: [10.1, 16.6]) in the vemurafenib arm and 16.7 months (range: [16.3, 18.4]) in the Combo 450 arm.

Efficacy Results – Key Secondary Endpoints

Table 29 presents the analysis of PFS for the Combo 450 arm compared with the encorafenib arm. The Combo 450 arm did not demonstrate a significant improvement in progression-free survival when compared to the encorafenib arm, with a two-sided stratified log-rank test p-value of 0.0513.

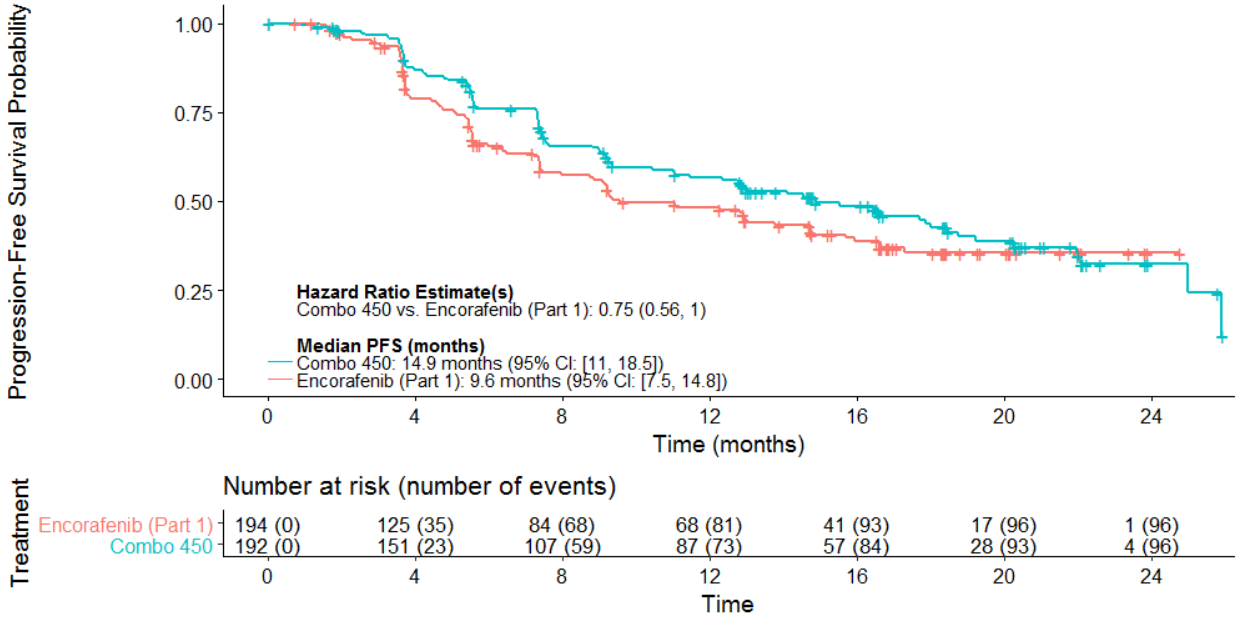
The estimated median PFS times were 14.9 months (95% CI: [11.0, 18.5]) for the Combo 450 arm and 9.6 (95% CI: [8.7, 14.8]) for the encorafenib arm. The stratified hazard ratio of PFS for the Combo 450 arm compared to the encorafenib arm was 0.75 (95% CI: [0.56, 1.00]). Figure 11 shows the PFS curves, estimated using the Kaplan-Meier method.

Table 29: Progression-Free Survival in the ITT Population for Part 1 of COLUMBUS (Combo 450 vs. Encorafenib)

	Encorafenib N = 191	Combo 450 N = 192
Number of events (%)	96 (50)	98 (51)
Censored (%)	95 (50)	94 (49)
Median PFS[1] in months (95% CI)	9.6 (7.5, 14.8)	14.9 (11.0, 18.5)
Hazard Ratio (95% CI)[2]	0.75 (0.56, 1.00)	
P-value[3]	0.0513	

Source: FDA Analysis
[1] BIRC central review
[2] Estimated with the Cox proportional hazards model stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1).
[3] Two-sided p-value estimated with the log-rank test stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1).

Figure 11: Kaplan-Meier Plot of Progression-Free Survival in the ITT Population for COLUMBUS (Combo 450 vs. Encorafenib)



Source: FDA Analysis

Follow-up time was similar across arms, with a median potential follow-up time for PFS of 16.6 months (95% CI: [14.8, 18.1]) in the encorafenib arm and 16.7 months (95% CI: [16.3, 18.4]) in the Combo 450 arm.

Due to the pre-specified hierarchical testing procedure, formal testing was stopped after the test of PFS for the Combo 450 arm compared with the encorafenib arm.

Efficacy Results – Other Endpoints

The pre-specified analysis of Test 3 is shown below. As discussed in "Protocol Amendments," pooling of patients from Parts 1 and 2 may introduce bias into the analysis, as the parts were randomized separately and thus may yield imbalances in important patient characteristics. Patient baseline characteristics, demographics, and protocol deviations including the pooled encorafenib group can be found in Section 19.3.

Table 30 presents the analysis of PFS for the encorafenib (Parts 1 + 2) group compared with the Combo 300 arm. The Combo 300 arm exhibited a numerical improvement in progression-free survival when compared to the encorafenib (Parts 1 + 2) group, though no formal test was performed due to hierarchical testing rules.

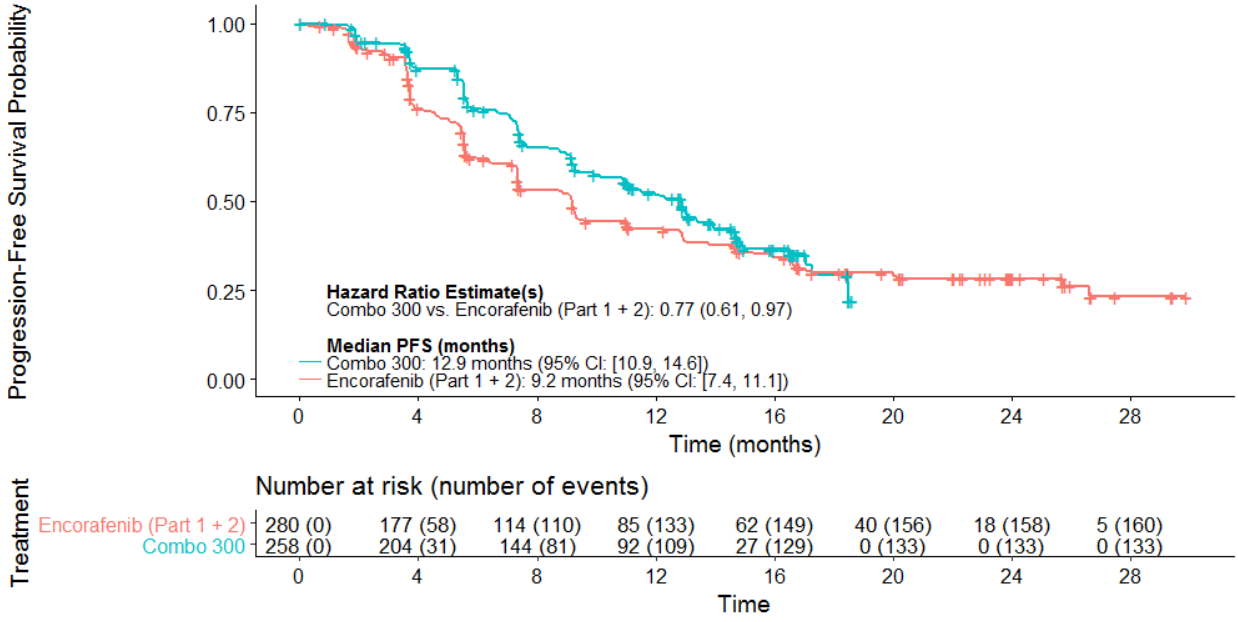
The estimated median PFS times were 12.9 months (95% CI: [10.1, 14.0]) for the Combo 300 arm and 9.2 (95% CI: [7.4, 11.0]) in the encorafenib (Parts 1 + 2) group. The stratified hazard ratio of PFS for the Combo 300 arm compared to the encorafenib (Parts 1 + 2) group was 0.77 (95% CI: [0.61, 0.97]). Figure 12 shows the PFS curves, estimated using the Kaplan-Meier method.

Table 30: Progression-Free Survival in the ITT Population for COLUMBUS (Combo 300 vs. Pooled Encorafenib Group)

	Encorafenib 300 (Parts 1 + 2) N = 280	**Combo 300 N = 258**
Number of events (%)	160 (57)	133 (52)
Censored (%)	120 (43)	125 (48)
Median PFS[1] in months (95% CI)	9.2 (7.4, 11.0)	12.9 (10.1, 14.0)
Hazard Ratio (95% CI)[2]	0.77 (0.61, 0.97)	

Source: FDA Analysis
[1] BIRC central review
[2] Estimated with the Cox proportional hazards model stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1).

Figure 12: Kaplan-Meier Plot of Progression-Free Survival in the ITT Population for COLUMBUS (Combo 300 vs. Pooled Encorafenib Group)



Source: FDA Analysis

Follow-up time was longer in the encorafenib (Parts 1 + 2) group, with a median potential follow-up time for PFS of 18.5 months (95% CI: [16.8, 22.0]) in the encorafenib (Parts 1 + 2) group and a median follow-up time of 13.9 months (range: [12.9, 14.7]) in the Combo 300 arm. This longer follow-up in the encorafenib (Parts 1 + 2) group is a result of randomization occurring later for Part 2 than for Part 1. Part 1 patients were randomized between December 30, 2013 and April 10, 2015 and Part 2 patients were randomized between March 19, 2015, and November 12, 2015. The median potential follow-up time for PFS for patients receiving encorafenib was 20.3 months (95% CI: [19.6, 23.3]) for patients in Part 1 and 14.8 months (95% CI: [14.7, 16.6]) for patients in Part 2.

Reviewer's comment: A sensitivity analysis that utilizes only patients from Part 2 for this analysis is presented in "Sensitivity Analyses." The sensitivity analysis is underpowered, as the trial was powered for the analysis of Test 3. The sensitivity analysis also shows a numerical trend of improved PFS in the Combo 300 arm.

Table 31 presents a preliminary analysis of OS for the Combo 450 arm compared with the vemurafenib arm. At the time of submission, Array was blinded to OS data. The data reviewed here was submitted by the DMC. The number of events required for an interim analysis (232) had not been reached at the time of data cut-off for Part 1. The analysis presented is based on 157 events.

The Combo 450 arm exhibited a numerical improvement in overall survival when compared to the vemurafenib arm, though no formal test was performed due to hierarchical testing rules.

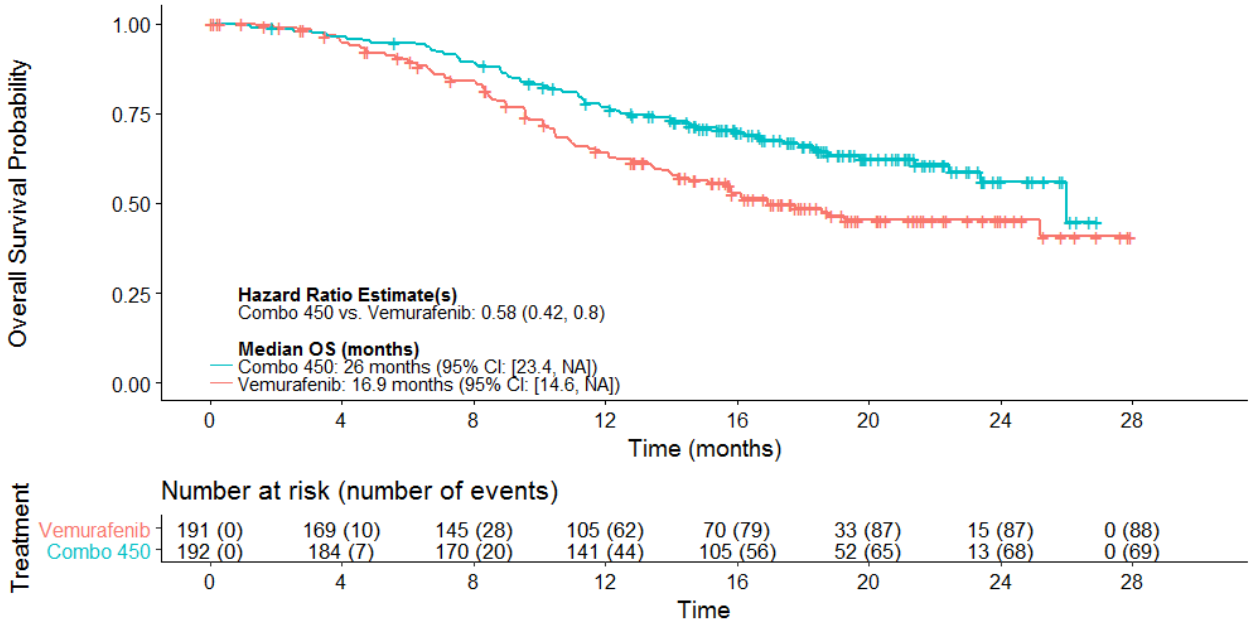
The estimated median OS times were 26.0 months (95% CI: [23.4, NE]) for the Combo 450 arm and 16.9 months (95% CI: [14.6, NE]) for the vemurafenib arm. The hazard ratio of OS for the Combo 450 arm compared to the vemurafenib arm was 0.58 (95% CI: [0.42, 0.80]). Figure 13 shows the OS curves, estimated using the Kaplan-Meier method.

Table 31: Overall Survival, as Reported by the DMC, in the ITT Population for Part 1 of COLUMBUS (Combo 450 vs. Vemurafenib)

	Vemurafenib N = 191	Combo 450 N = 192
Number of events (%)	88 (46)	69 (36)
Censored (%)	103 (54)	123 (64)
Median OS in months (95% CI)	16.9 (14.6, NE[1])	26.0 (23.4, NE[1])
Hazard Ratio (95% CI)[2]	0.58 (0.42, 0.80)	

Source: FDA Analysis
[1] NE: Not estimable.
[2] Estimated with the Cox proportional hazards model stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1).

Figure 13: Kaplan-Meier Plot of Overall Survival in the ITT Population for Part 1 of COLUMBUS (Combo 450 vs. Vemurafenib)



Source: FDA Analysis

Follow-up time was similar across arms, with a median potential follow-up time for OS of 19.4 months (95% CI: [18.5, 20.5]) in the Combo 450 arm and 18.2 months (range: [17.4, 19.5]) in the vemurafenib arm.

Reviewer's comment: At the time of submission, Array was blinded to OS data. Consequently, this analysis was not included in the CSR. The above analysis is the product of the reviewer only and not a confirmation of sponsor analyses.

Durability of Response

Table 32 presents the confirmed ORR and DOR for each arm in Part 1 of COLUMBUS. ORR was defined as the proportion of patients with best objective response of complete response (CR) or partial response (PR). ORR had to be confirmed, as defined for CR and PR below:

- CR: at least two determinations of CR at least 4 weeks apart before progression
- PR: at least two determinations of PR or better at least 4 weeks apart before progression.

Table 32: Confirmed ORR and DOR Results from Part 1 of COLUMBUS

	Combo 450 N = 192	**Encorafenib N = 194**	**Vemurafenib N = 191**
ORR[1]	63%	51%	40%
(95% CI)[2]	(56%, 70%)	(43%, 58%)	(33%, 48%)
CR	8%	5%	6%
PR	55%	45%	35%
Median DOR, months	16.6	14.9	12.3
(95% CI)	(12.2, 20.4)	(11.1, NE)	(6.9, 16.9)

Source: FDA Analysis
[1] BIRC central review
[2] Estimated using the Clopper-Pearson method

Table 33 presents the confirmed ORR and DOR for the groups in the Part 2 analysis of COLUMBUS.

Table 33: Confirmed ORR and DOR Results from Part 2 of COLUMBUS

	Combo 300 N = 258	**Encorafenib (Part 2) N = 86**
ORR[1]	66%	50%
(95% CI)[2]	(60%, 72%)	(39%, 61%)
CR	8%	3%
PR	58%	47%
Median DOR, months	12.7	7.5
(95% CI)	(9.3, 15.1)	(5.6, 14.0)

Source: FDA Analysis
[1] BIRC central review
[2] Estimated using the Clopper-Pearson method

Table 34 shows the confirmed ORR and DOR by part for the encorafenib arms in COLUMBUS. ORR seems to be similar between arms. DOR was longer in Part 1, with an estimated median

DOR of 15.2 months (95% CI: [11.1, NE]) in part 1 and 7.5 months (95% CI: [5.6, 14.0]) in part 2. As stated above follow-up was longer for part 1.

Table 34: Confirmed ORR and DOR Results for the Encorafenib Arms in Parts 1 and 2 of COLUMBUS

	Encorafenib (Part 1) N = 194	Encorafenib (Part 2) N = 86
ORR[1]	51%	50%
(95% CI)[2]	(43%, 58%)	(39%, 61%)
CR	6%	3%
PR	44%	47%
Median DOR, months	15.2	7.5
(95% CI)	(11.1, NE)	(5.6, 14.0)

Source: FDA Analysis
[1] BIRC central review
[2] Estimated using the Clopper-Pearson method

Efficacy results for ORR and DOR which include the pooled encorafenib group may be found in Section 19.3.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The following PRO analyses were pre-specified in the SAP. However, no type I error was allocated to any of the PRO analyses, and consequently these analyses are considered exploratory only.

In COLUMBUS, health quality of life data was collected via three instruments: the FACT-M, EQ-5D-5L, and EORTC QLQ-C30. The primary PRO analysis in COLUMBUS was to assess the difference in distribution of time to definitive 10% deterioration in the FACT-M melanoma subscale between the treatment arms in ITT population. The time to definitive 10% deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% relative to baseline worsening of the corresponding scale score with no later improvement above this threshold observed while on treatment or death due to any cause. The censoring rules were as follows:

- Patients who had definitive deterioration after more than twice the planned period between two assessments since the last assessment were censored at the date of their last available questionnaire.
- Patients receiving any further anti-neoplastic therapy before definitive deterioration were censored at the date of their last assessment before starting this therapy.
- Patients that had not worsened as of the cut-off date for the analysis were censored at the date of their last assessment before the cut-off.
- Patients with no baseline assessment or no postbaseline assessment performed were censored at the randomization date.

Compliance was assessed as the percentage of patients who completed the full or part of the FACT-M questionnaire while on study. Compliance was calculated for patients still at risk. A patient was considered "at-risk" if they were still receiving treatment or were in post-treatment follow-up on the protocol-scheduled PRO assessment date. Compliance by cycle in Part 1 is shown in Table 35.

Table 35: FACT-M Compliance Summary by Time Window and Treatment (Part 1)

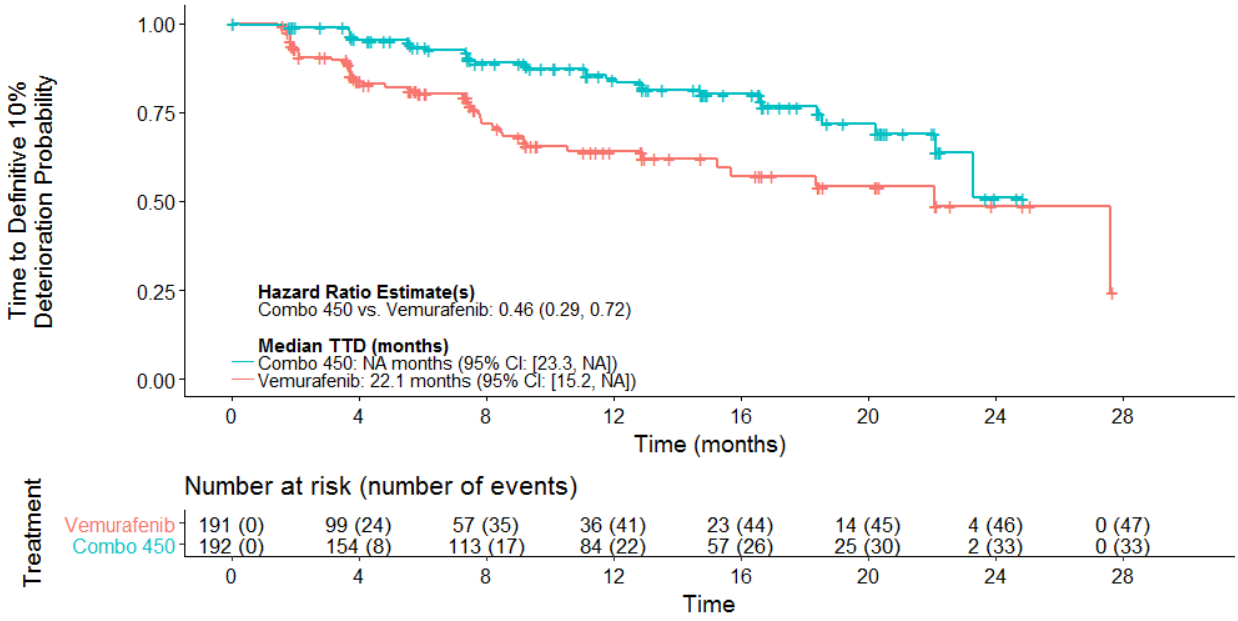
Visit	Combo 450		Encorafenib (Part 1)		Vemurafenib	
	Number of Patients Still on Study	Number of Patients Who Filled Out Instrument n (%)[1]	Number of Patients Still on Study	Number of Patients Who Filled Out Instrument n (%)[1]	Number of Patients Still on Study	Number of Patients Who Filled Out Instrument n (%)[1]
Baseline	192	165 (86)	194	159 (82)	191	160 (84)
Cycle 3 Day 1	185	168 (91)	186	168 (90)	181	160 (88)
Cycle 5 Day 1	174	153 (88)	157	145 (92)	145	128 (88)
Cycle 7 Day 1	161	143 (89)	132	120 (91)	110	101 (92)
Cycle 9 Day 1	139	122 (88)	100	88 (88)	87	80 (92)
Cycle 11 Day 1	121	109 (90)	86	79 (92)	63	56 (89)
Cycle 13 Day 1	104	94 (90)	77	71 (92)	49	48 (98)
Cycle 15 Day 1	94	83 (88)	72	62 (86)	40	36 (90)
Cycle 17 Day 1	83	76 (92)	62	53 (85)	34	30 (88)
Cycle 19 Day 1	66	56 (85)	47	44 (94)	29	25 (86)
Cycle 21 Day 1	46	39 (85)	36	33 (92)	22	20 (91)
Cycle 23 Day 1	31	26 (84)	20	20 (100)	16	15 (94)
Cycle 25 Day 1	22	18 (82)	11	9 (82)	11	10 (91)

Source: FDA Analysis
[1] Includes instruments fully or partially completed

Compliance was similar across arms for the first 25 cycles of treatment. At Cycle 25 Day 1, 22 patients were on study in the Combo 450 arm, 11 patients were on study in the encorafenib arm, and 11 patients were on study in the vemurafenib arm.

The estimated median time to definitive 10% deterioration (TTD) in the FACT-M subscale was not estimable (95% CI: [23.3, NE]) for the Combo 450 arm and 22.1 months (95% CI: [15.2, NE]) in the vemurafenib arm. The stratified hazard ratio of TTD for the Combo 450 arm compared to the vemurafenib arm was 0.46 (95% CI: [0.29, 0.72]). Figure 14 shows the TTD curves, estimated using the Kaplan-Meier method.

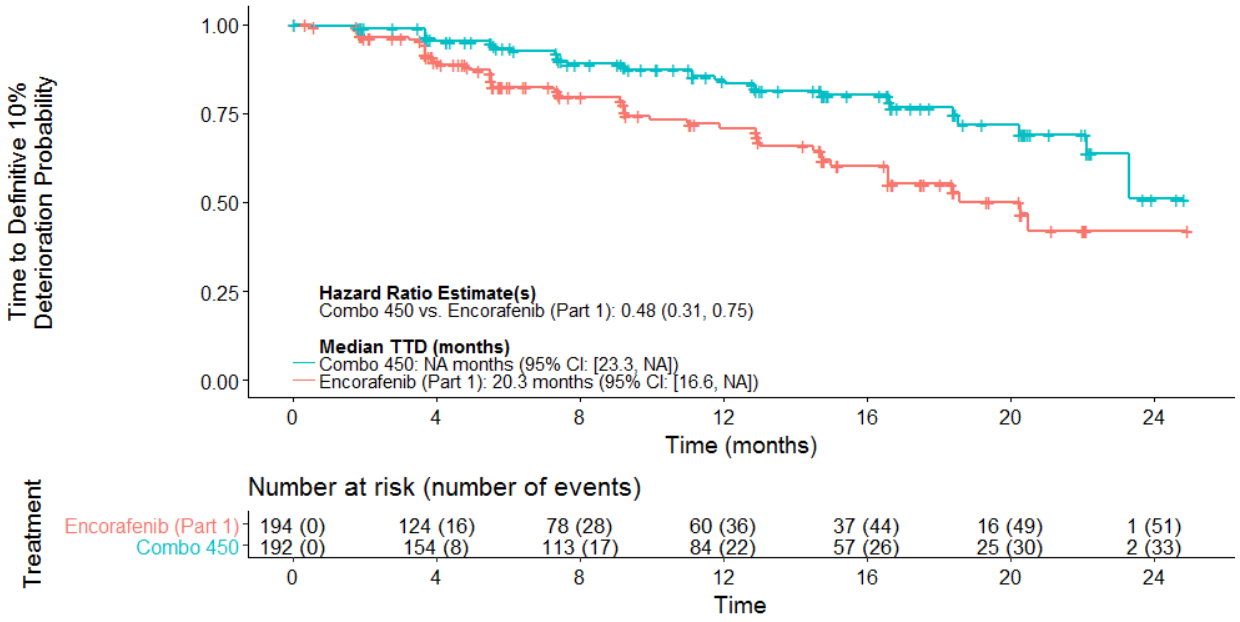
Figure 14: Time to Definitive 10% Deterioration in the FACT-M Subscale – Combo 450 vs. Vemurafenib (Part 1)



Source: FDA Analysis

The estimated median time to 10% deterioration (TTD) in the FACT-M subscale was not estimable (95% CI: [23.3, NE]) for the Combo 450 arm and 20.3 months (95% CI: [16.6, NE]) in the encorafenib arm. The stratified hazard ratio of TTD for the Combo 450 arm compared to the encorafenib arm was 0.48 (95% CI: [0.31, 0.75]). Figure 15 shows the TTD curves, estimated using the Kaplan-Meier method.

Figure 15: Time to Definitive 10% Deterioration in the FACT-M Subscale – Combo 450 vs. Encorafenib (Part 1)



Source: FDA Analysis

Compliance by cycle in Part 2 is shown in Table 36.

Table 36: FACT-M Compliance Summary by Time Window and Treatment (Part 2)

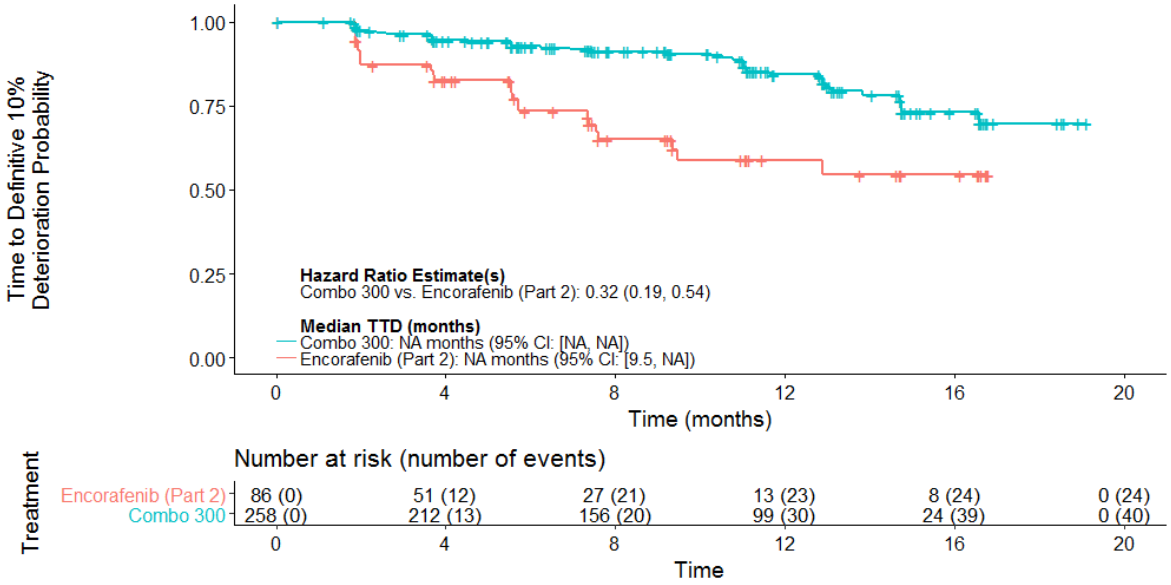
Visit	Combo 300		Encorafenib (Part 2)	
	Number of Patients Still on Study	Number of Patients Who Filled Out Instrument n (%)[1]	Number of Patients Still on Study	Number of Patients Who Filled Out Instrument n (%)[1]
Baseline	258	237 (92)	86	83 (97)
Cycle 3 Day 1	254	233 (92)	77	69 (90)
Cycle 5 Day 1	242	220 (91)	69	62 (90)
Cycle 7 Day 1	219	197 (90)	55	53 (96)
Cycle 9 Day 1	189	172 (91)	44	44 (100)
Cycle 11 Day 1	164	152 (93)	36	32 (89)
Cycle 13 Day 1	148	139 (94)	30	27 (90)
Cycle 15 Day 1	111	101 (91)	20	18 (90)
Cycle 17 Day 1	74	68 (92)	16	14 (88)
Cycle 19 Day 1	35	29 (83)	9	9 (100)
Cycle 21 Day 1	16	13 (81)	2	1 (50)

Source: FDA Analysis
[1] Includes instruments fully or partially completed

Compliance was similar across arms for the first 17 cycles of treatment. At Cycle 17 Day 1, 74 patients were on study in the Combo 300 arm, and 16 patients were on study in the encorafenib arm.

The estimated median time to 10% deterioration (TTD) in the FACT-M subscale was not estimable (95% CI: [NE, NE]) for the Combo 300 arm and not estimable (95% CI: [9.5, NE]) in the encorafenib arm. The stratified hazard ratio of TTD for the Combo 300 arm compared to the encorafenib arm was 0.32 (95% CI: [0.19, 0.54]). Figure 16 shows the TTD curves, estimated using the Kaplan-Meier method.

Figure 16: Time to Definitive 10% Deterioration in the FACT-M Subscale – Combo 300 vs. Encorafenib (Part 2)



Source: FDA Analysis

Compliance was similar for the EQ-5D-5L and EORTC QLQ-C30. Time to definitive deterioration was similar for the EORTC QLQ-C30. A mixed effect model for repeated measures (MMRM) was used to compare the treatment arms in terms of change from baseline the domain score over time (FACT-M melanoma subscale, index score of the EQ-5D-5L and global health status/QoL scale score). The results from the mixed effect model support the analyses results described above.

Other descriptive analyses of the FACT-M may be found in Section 19.3.

Additional Analyses Conducted on the Individual Trial

Sensitivity Analyses for Test 2

Array pre-specified a variety of sensitivity analyses for the PFS endpoints. Because test 2 failed

with a non-significant p-value, the superiority of Combo 450 to encorafenib in PFS was not clearly demonstrated. To assess the robustness of this result, we present a few pre-specified sensitivity analyses. Results of other pre-specified sensitivity analyses yield similar results. Array pre-specified a sensitivity analysis for PFS that would repeat the primary analysis with a censoring rule that backdates events occurring after one or more missing tumor assessments. Events were to be backdated to the assessment following the last adequate assessment: 8 weeks (or 12 weeks if the patient had been on treatment long enough) after the last adequate tumor assessment. Table 37 summarizes these results.

Table 37: Progression-Free Survival in the ITT for Part 1 of COLUMBUS using "Backdated" Assessments (Combo 450 vs. Encorafenib)

	Encorafenib N = 191	**Combo 450 N = 192**
Number of events (%)	102 (53)	102 (53)
Censored (%)	89 (47)	91 (47)
Median PFS in months (95% CI)	9.3 (7.4, 12.9)	14.1 (9.4, 18.0)
Hazard Ratio (95% CI)[1]	0.74 (0.56, 0.98)	

Source: FDA Analysis
[1] Estimated with the Cox proportional hazards model stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1).

This analysis corrects for an imbalance in missed assessments between arms when the missed assessments are related to progression. If missed assessments are related to progression, the primary analysis may be biased, as patients who miss two or more assessments are censored at the last adequate assessment, even if they progress after the second missed assessment. In this scenario, the "backdated" analysis may more accurately measure the true treatment effect. In COLUMBUS, 6 patients had an event after two or more missed assessments on the encorafenib arm, and 4 patients on the Combo 450 arm.

Additional sensitivity analyses for Test 2 may be found in the Appendix.

Sensitivity Analysis for Test 3

Array also pre-specified a sensitivity analysis for test 3. As stated in the SAP v.4, "Stratified analyses for PFS (i.e. log-rank-test, Kaplan-Meier estimates and plots and Cox regression) will be repeated with data only for patients enrolled during Part 2 of the study. This will be performed separately for data assessed by BIRC and locally." This analysis was intended to address the fact that the analysis of test 3 included patients randomized to encorafenib in Part 1, and thus were not randomized concurrently with patients in the Combo 300 arm. Table 38 summarizes the results of this analysis.

Table 38: Sensitivity Analysis for Progression-Free Survival in the ITT Population for Part 2 of COLUMBUS (Combo 300 vs. Encorafenib)

	Encorafenib N = 86	Combo 300 N = 258
Number of events (%)	96 (50)	133 (52)
Censored (%)	56 (65)	125 (48)
Median PFS in months (95% CI)	7.4 (5.6, 9.2)	12.9 (10.1, 14.0)
Hazard Ratio (95% CI)[1]	0.57 (0.41, 0.78)	

Source: FDA Analysis
[1] Estimated with the Cox proportional hazards model stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1).

The estimated median PFS time for the encorafenib arm in Part 2 was 7.4 months (95% CI: [5.6, 9.2]). In Part 1, the estimated median PFS time for the encorafenib arm was 9.6 months (95% CI: [7.4, 14.8]). As discussed in the main efficacy results, follow-up time was longer in Part 1 than in Part 2. Additionally, the parts were randomized separately, yielding patient populations with slightly different demographics and baseline characteristics.

8.1.4. LOGIC2 – Study Results

Patient Disposition

Table 39 summarizes the disposition of patients who were naïve to treatment with BRAF inhibitors (Group A) in Part 1 of LOGIC2.

Table 39: Patient Disposition in Group A of Part 1 of LOGIC2

	Combo 450 N = 75 n (%)
Treatment received (%)	
YES	75 (100)
Primary reason for treatment discontinuation in Part 1 (%)	
ADVERSE EVENT	3 (4)
COMPLETED	0 (0)
DEATH	5 (7)
PHYSICIAN DECISION	1 (1)
PROGRESSIVE DISEASE	19 (25)
WITHDRAWAL BY PARENT/GUARDIAN	3 (4)
TREATMENT ONGOING	44 (59)
Treatment status at the end of Part 1 (%)	
TREATMENT ONGOING	44 (59)
TREATMENT DISCONTINUED	31 (41)

Source: FDA Analysis

Demographic Characteristics

Table 40 summarizes the patient demographics of patients who were naïve to treatment with BRAF inhibitors (Group A) in Part 1 of LOGIC2.

Table 40: Patient Demographics in Group A of Part 1 of LOGIC2

	Combo 450 N=75
Age (mean (sd))	55.3 (12.9)
Age Category (%)	
< 65	57 (76)
>= 65	18 (24)
Sex (%)	
F	28 (37)
M	47 (63)
Race (%)	
ASIAN	1 (1)
WHITE	74 (99)
ECOGBL (%)	
0	55 (73)
1	19 (25)
2	1 (1)
MISSING	0 (0)

Source: FDA Analysis

Baseline Disease Characteristics

Table 41 summarizes the patient and disease characteristics of patients who were naïve to treatment with BRAF inhibitors (Group A) in Part 1 of LOGIC2.

Table 41: Patient and Disease Characteristics in LOGIC2

	Combo 450 N = 75
Primary site of cancer (%)	
SKIN	62 (83)
UNKNOWN	5 (7)
OTHER	8 (11)
MISSING	0 (0)
Stage at time of study entry (%)	
STAGE IIIC	5 (7)
STAGE IV	60 (80)
STAGE IVA	2 (3)
STAGE IVB	8 (11)
MISSING	0 (0)
Number of organs involved at baseline (%)	
1	13 (17)
2	14 (19)
3	17 (23)
>3	31 (41)
Missing	0 (0)
LDH at baseline (%)	
<= ULN	21 (28)
> ULN	14 (19)
MISSING	40 (53)

Source: FDA Analysis

Efficacy Results – Primary Endpoint

As stated in "Study Endpoints," a primary efficacy endpoint for Part 1 was not defined in the study protocol. ORR as determined by investigator is presented here, as it was the primary endpoint for Part 2.

Table 42 presents the confirmed ORR and DOR for Group A of Part 1 of LOGIC2. Confirmation of complete response (CR) or partial response (PR) had to be at least 4 weeks apart from the previous radiological assessment.

Table 42: Confirmed ORR and DOR Results for Group A of Part 1 of LOGIC2

	Combo 450 N = 75
ORR[1]	69%
(95% CI)[2]	(58%, 80%)
CR	1%
PR	68%
Median DOR, months	8.5
(95% CI)	(6.7, 9.9)

Source: FDA Analysis
[1] Assessed by investigator
[2] Estimated using the Clopper-Pearson method

The median duration of potential follow-up time for confirmed ORR was 9.4 months (95% CI: [7.1, 10.6]) for patients naïve to BRAF inhibitors (Group A) of Part 1.

Efficacy Results – Other Endpoints

In LOGIC2, PFS was assessed by investigator. The estimated median PFS time for Group A of Part 1 was 9.5 months (95% CI: [8.0, 11.0]). The median duration of potential follow-up time for PFS was 9.4 months (95% CI: [7.1, 10.6]) for these patients.

As stated in "Primary Endpoints," median DOR for ORR for Group A of Part 1 was 8.5 months (95% CI: [6.7, 9.9]).

8.1.5. Assessment of Efficacy Across Trials

Primary Endpoints

COLUMBUS demonstrated that Combo 450 had a statistically significant effect on PFS as assessed by BIRC when compared to vemurafenib. The estimated median PFS times were 14.9 months (95% CI: [11.0, 18.5]) for the Combo 450 arm and 7.3 months (95% CI: [5.6, 8.2]) in the vemurafenib arm. The hazard ratio of PFS for the Combo 450 arm compared to the vemurafenib arm was 0.54 (95% CI: [0.41, 0.71]).

While PFS was also measured in LOGIC2, time to event endpoints such as PFS are not interpretable in single arm studies. Furthermore, baseline differences in the study population and a shorter median follow-up time on the LOGIC2 study compared to the COLUMBUS study preclude cross-study observational comparisons with respect to PFS.

Secondary and Other Endpoints

COLUMBUS provided evidence on the treatment effect of Combo 450 on PFS when compared to encorafenib. The estimated median PFS times were 14.9 months (95% CI: [11.0, 18.5]) for the Combo 450 arm and 9.6 (95% CI: [8.7, 14.8]) in the encorafenib arm. The hazard ratio of PFS

for the Combo 450 arm compared to the encorafenib arm was 0.75 (95% CI: [0.56, 1.00]). This effect size was similar when estimated under various sensitivity analyses.

COLUMBUS also measured ORR. In COLUMBUS, the confirmed ORR for the Combo 450 arm was 63% (95% CI: [56%, 70%]) with an estimated median duration of response of 16.6 months (95% CI: [12.2, 20.4]) and 40% (95% CI: [33%, 48%]) with a duration of response 12.3 months (95% CI: [6.9, 16.9]) in the vemurafenib arm.

In LOGIC2, the ORR was assessed by investigator. The confirmed ORR for the BRAF inhibitor-naïve patients treated with Combo 450 was 69% (95% CI: [58%, 80%]) with a median duration of response of 8.5 months (95% CI: [6.7, 9.9]).

ORR in patients who were naïve to BRAF-inhibitors and treated with Combo 450 seems to be similar across trials. Differences in duration of response may be due to differences in length of follow-up or differences in patient populations.

Subpopulations

Tables for subgroup comparisons are shown in the figures below. Table 43 shows PFS comparisons of Combo 450 vs. vemurafenib from Part 1 by subgroup.

Table 43: Comparisons of Combo 450 vs. Vemurafenib in Part 1 by Subgroup

Subgroup	Combo 450: #Events/N	Vemurafenib: #Events/N	HR (95% CI)
Sex			
M	63/115	61/111	0.62 (0.44, 0.89)
F	35/77	45/80	0.5 (0.32, 0.79)
Disease Stage			
IVM1c	72/123	73/125	0.56 (0.4, 0.78)
IIIB, IIIC, IVM1a or IVM1b	26/69	33/66	0.56 (0.34, 0.94)
Prior 1st line Immunotherapy			
Y	5/8	4/7	0.4 (0.1, 1.64)
N	93/184	102/184	0.59 (0.44, 0.78)
ECOG			
1	37/55	33/51	0.67 (0.42, 1.08)
0	61/136	73/140	0.52 (0.37, 0.74)
BRAF Mutation			
V600K	8/22	15/23	0.27 (0.11, 0.68)
V600E	90/170	91/168	0.64 (0.48, 0.85)
Region			
Other	8/14	11/15	0.64 (0.26, 1.6)
North America	8/17	10/17	0.42 (0.16, 1.1)
Europe	80/156	83/153	0.58 (0.42, 0.79)
Australia	2/5	2/6	0.63 (0.06, 6.97)
Race			
Non-Caucasian	5/11	15/25	0.52 (0.19, 1.43)
Caucasian	93/181	91/166	0.59 (0.44, 0.79)
Baseline Brain Metasteses			
Y	5/9	1/3	1.34 (0.15, 11.79)
N	93/183	105/188	0.57 (0.43, 0.75)
Age			
>=65	29/60	26/51	0.66 (0.39, 1.12)
<65	69/132	80/140	0.55 (0.4, 0.77)
Overall			
	98/192	106/191	0.58 (0.44, 0.77)

Source: FDA Analysis

Table 44 shows PFS comparisons of Combo 450 vs. encorafenib from Part 1 by subgroup.

Table 44: Comparisons of Combo 450 vs. Encorafenib in Part 1 by Subgroup

Subgroup	Combo 450: #Events/N	Encorafenib (Part 1): #Events/N	HR (95% CI)
Sex			
M	63/115	58/108	0.81 (0.56, 1.16)
F	35/77	38/86	0.8 (0.5, 1.26)
Disease Stage			
IVM1c	72/123	68/120	0.68 (0.49, 0.96)
IIIB, IIIC, IVM1a or IVM1b	26/69	28/74	0.95 (0.56, 1.63)
Prior 1st line Immunotherapy			
Y	5/8	5/11	0.81 (0.23, 2.83)
N	93/184	91/183	0.81 (0.6, 1.08)
ECOG			
1	37/55	31/53	0.79 (0.49, 1.28)
0	61/136	65/141	0.79 (0.56, 1.13)
BRAF Mutation			
V600K	8/22	8/19	0.53 (0.2, 1.44)
V600E	90/170	87/173	0.86 (0.64, 1.15)
Region			
Other	8/14	10/13	0.99 (0.39, 2.52)
North America	8/17	10/27	0.84 (0.33, 2.13)
Europe	80/156	74/150	0.8 (0.58, 1.09)
Australia	2/5	2/4	1.11 (0.15, 7.91)
Race			
Non-Caucasian	5/11	12/20	0.61 (0.21, 1.73)
Caucasian	93/181	84/174	0.84 (0.63, 1.13)
Baseline Brain Metasteses			
Y	5/9	7/8	0.31 (0.09, 1.07)
N	93/183	89/186	0.84 (0.63, 1.12)
Age			
>=65	29/60	21/40	0.71 (0.4, 1.25)
<65	69/132	75/154	0.82 (0.59, 1.15)
Overall			
	98/192	96/194	0.81 (0.61, 1.07)

Source: FDA Analysis

Table 45 shows PFS comparisons of Combo 300 vs. encorafenib from Part 2.

Table 45: Comparisons of Combo 300 vs. Encorafenib in Part 2 by Subgroup

Subgroup	Combo 300: #Events/N	Encorafenib (Part 2): #Events/N	HR (95% CI)
Sex			
M	79/151	29/44	0.57 (0.37, 0.88)
F	54/107	27/42	0.55 (0.35, 0.88)
Disease Stage			
IVM1c	95/172	44/58	0.5 (0.35, 0.72)
IIIB, IIIC, IVM1a or IVM1b	38/86	12/28	0.8 (0.42, 1.55)
Prior 1st line Immunotherapy			
Y	7/18	3/5	0.19 (0.04, 0.83)
N	126/240	53/81	0.6 (0.43, 0.82)
ECOG			
1	39/70	18/23	0.43 (0.25, 0.77)
0	93/187	38/63	0.6 (0.41, 0.88)
BRAF Mutation			
V600K	23/34	3/6	2.36 (0.68, 8.2)
V600E	110/224	53/80	0.5 (0.36, 0.7)
Region			
Other	18/43	10/12	0.4 (0.19, 0.88)
North America	7/14	1/2	0.15 (0.01, 1.7)
Europe	108/201	45/71	0.62 (0.44, 0.88)
Australia	0/0	0/1	1 (1, 1)
Race			
Non-Caucasian	5/22	7/8	0.1 (0.03, 0.35)
Caucasian	128/236	49/78	0.64 (0.46, 0.9)
Baseline Brain Metasteses			
Y	5/7	2/2	0.83 (0.13, 5.14)
N	128/251	54/84	0.56 (0.4, 0.76)
Age			
>=65	43/83	16/26	0.69 (0.39, 1.23)
<65	90/175	40/60	0.51 (0.35, 0.75)
Overall			
	133/258	56/86	0.56 (0.41, 0.77)

Source: FDA Analysis

The subgroup analyses do not show any outliers in the treatment effect across subgroups for any of the treatment comparisons.

8.1.6. Integrated Assessment of Effectiveness

The data from COLUMBUS showed a statistically significant improvement in PFS for Combo 450 when compared to vemurafenib. Data collected from other trials further characterize the efficacy of Combo 450, and support the observed ORR in COLUMBUS.

Supportive data for the contribution of binimetinib to the combination was collected in Parts 1 and 2 of COLUMBUS. Part 1 suggested a trend for improved PFS for the Combo 450 arm when compared to the encorafenib arm, though this comparison did not reach statistical significance. Part 2 suggested a trend for improved PFS for the Combo 300 arm when compared to the encorafenib arm.

CDTL Comment: Part 1 COLUMBUS Study met its primary endpoint, demonstrating that the combination of encorafenib (450 mg daily) and binimetinb (45 mg twice daily) was associated with a clinically and statistically significant improvement in PFS compared to vemurafenib as an

active control. However, per the FDA's Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination, the development program must establish that each drug contributes to the overall treatment effect. As a class, MEK inhibitors have modest single agent activity in BRAF-mutated melanoma. For example, while trametinb (a MEK inhibitor) has approval as a single agent in unresectable or metastatic melanoma based on a randomized trial demonstrating an improvement in PFS compared to chemotherapy, trametinib is associated with an ORR of 22%, while dabrafenib (a BRAF inhibitor) yields an ORR of 51% and the combination of the two an ORR of 66% (trametinib USPI). The FDA thus did not consider it ethical to require the applicant to demonstrate the necessity of encorafenib to the observed treatment effect by including a binimetinb monotherapy control arm on COLUMBUS.

By contrast, given the high response rates and durability of responses that have been observed with BRAF inhibitors in BRAF-mutated melanoma as a class, the FDA considered it necessary for the applicant to demonstrate the necessity of binimetinb to the observed treatment effect by including an encorafenib monotherapy control arm. This was complicated by the inability to dose encorafenib monotherapy at more than 300 mg daily due to toxicities that are mitigated by the addition of binimetinb as described earlier in this review.

The Combo 450 arm demonstrated a numerical, but not statistically significant, improvement in PFS when compared to the encorafenib monotherapy arm, with a stratified hazard ratio of 0.75 (95% CI: [0.56, 1.00]), and a p-value of 0.0513. The marginal failure of this endpoint precluded further formal hypothesis testing due to hierarchical testing rules, including a comparison of the Combo 300 arm to encorafenib monotherapy on Part 2 of COLUMBUS. However, the Combo 300 arm exhibited a numerical improvement in PFS when compared to encorafenib monotherapy, with a stratified hazard ratio of 0.77 (95% CI: [0.61, 0.97]). Although it was not formally demonstrated, the consistency of these results across two trial stages provides a reasonable degree of confidence using a totality of the evidence approach that the addition of binimetinib to encorafenib prolongs PFS compared to encorafenib alone, and that both drugs are required to achieve the observed treatment effect.

8.2. **Review of Safety**

8.2.1. **Safety Review Approach**

Table 46 and Table 47 list the trials submitted to the NDA by the applicant contributing safety data to the analysis of the Combo 450 regimen. The primary trial characterizing the safety of this regimen was COLUMBUS Part 1. Seven patients who were randomized in Part 1 withdrew from the study prior to receiving any study treatment (5 patients in the vemurafenib arm and 2 in the encorafenib monotherapy arm). Only patients who received at least one dose of study drug are included in the safety analysis set. The safety analysis set for COLUMBUS Part 1 comprises 570 patients distributed as follows: 192 patients in the Combo 450 arm, 192 patients in the encorafenib monotherapy arm, and 186 patients in the vemurafenib arm.

The submission also included supportive safety data from Part 2 of COLUMBUS that compared a Combo 300 regimen with encorafenib monotherapy 300 mg. For the integrated safety analysis, the application specified a pooled safety set consisting of a total of 274 patients with BRAF+ melanoma who received the Combo 450 regimen (Combo 450 Pool) and a pooled safety set consisting of a total of 433 patients with BRAF+ disease who were treated with a regimen of encorafenib at a dose ≥ 400 mg QD given with binimetinib 45 mg BID (Combo ≥400 Pool). The trials contributing to these pooled sets are shown in Table 46. Two single agent pooled data sets were also analyzed for encorafenib and binimetinib. The trials contributing to these pooled data sets are shown in Table 47. The encorafenib monotherapy pooled dataset consists of 217 patients with BRAF+ melanoma who received 300 mg encorafenib daily (Enc 300 Pool). The patients for this data set are drawn primarily from COLUMBUS Part 1 encorafenib monotherapy arm. The binimetinib pooled dataset consists of 429 patients with NRA+ or BRAF+ melanoma who received 45 mg binimetinib twice daily (Bini 45 pool). The patients for this dataset are drawn primarily from CMEK162A2301, a randomized controlled study of binimetinib compared to dactinomycin in patients with NRAS+ melanoma.

This review focuses primarily on the safety data from COLUMBUS Part 1. Section 8.2.3 summarizes the tolerability and toxicities observed in patients in the Combo 450 arm of COLUMBUS Part 1 when compared to the vemurafenib control arm. This section also includes presentation of analyses for the encorafenib monotherapy arm. The analyses of adverse events in this section is based on preferred term (PT) and MedDRA groupings. Section 8.2.4 evaluates the toxicity of Combo 450 in terms of adverse drug reactions (ADRs) which are submission specific composite events terms formed from PT grouping and are based on the applicant's analysis of adverse events of special interests (AESI) and known class effects of BRAF and MEK inhibitors.

The largest pooled combination safety set for combination therapy (Combo ≥ 400 pool) was analyzed to assess for the presence of any rare but serious adverse events observed only in larger populations. No new or more serious safety signals not identified in the analysis of the Combo 450 arm were identified in this assessment.

Table 46: Trials Submitted in Support of Safety Assessment of Combo 450 Regimen

Trial	Population Description	Treatment Group	Number of Patients Treated	Included in Combo 450 Pool N= 274	Included in Combo ≥ 400 Pool N= 433	Trial (cutoff date)
CMEK162B2391 COLUMBUS PART 1	BRAF + Melanoma	Combo 450	192	Y	Y	19 May 2016
		Enc 300 Part 1	192	N/A	N/A	
		Vemurafenib	168	N/A	N/A	
CMEK162B2391 COLUMBUS Part 2	BRAF + Melanoma	Combo 300	257	N	N	09 Nov 2016
		Enc 300 Part 2	84	N/A	N/A	
CLGX818X2109 (LOGIC2)	BRAF/MEK-treatment Naïve Melanoma	Combo 450	75 (Part 1 Group A)	Y	Y	18 Feb 2016
	BRAF/MEK-treatment Non-naïve melanoma	Combo 450	83 (Part 1 Group B/C Run-in)	N	Y	
CMEK162X2110	BRAF V600 – dependent advanced solid tumors	Combo 400	4	N	Y	31 Aug 2015
		Combo 450	21	Y (7 BRAF inhibitor naive melanoma)	Y	
		Combo 600	62	N	Y	

Source: Reviewer compiled from ISS Tables 1-1, 1-2, 1-3 (Submitted by Applicant to Module 5.3.5.3 June 30, 2017)

[1] Patients with diagnosis of melanoma who received encorafenib 450 mg QD with binimetinib 45 mg BID (267)

[2] Patients with diagnosis of melanoma who received encorafenib ≥ 400 mg QD with binimetinib 45 mg BID (350)

[3] Encorafenib 450 mg QD with binimetinib 45 mg BID

[4] Encorafenib monotherapy 300 mg QD

[5] Vemurafenib monotherapy 960 mg BID

[6] Encorafenib 300 mg QD with binimetinib 45 mg BID

Table 47: Trials Contributing to Pooled Single Agent Safety Data

Trial	Description	Patients	Trial (cutoff date)
Encorafenib 300 mg QD N=217			
CMEK162B2301 Enc 300 Part 1	BRAF + melanoma	192	19 May 2016
CMGX818X2101	BRAF + melanoma	10	18 Aug 2014
CLGX818X2102	BRAF V600+ melanoma	15	completed
Binimetinib 45 mg BID N=429			
CMEK162A2301	NRAS+ melanoma	269	18 Mar 2016
CMEK162X2201	BRAF+ melanoma	41	06 Nov 2015
	NRAS + melanoma	117	

Source: Reviewer compiled from ISS Table 1-3 (Submitted by Applicant to Module 5.3.5.3 June 30, 2017

Safety Database Quality Assessment

The quality of the safety database submitted was assessed. The accurate representation of the data submitted by the Investigators in the AE dataset was evaluated through a spot check of 15 randomly selected patients enrolled in Part 1. Comparison was made between the CRFs and the AE dataset. No omissions or inaccuracies were detected. The validity of the coding of verbatim reported adverse event terms to the MedDRA lower level terms was assessed through a comparison of almost 16,000 adverse events (AETERM) submitted with COLUMBUS to the lowest coded level, AELLT. This assessment identified 12 AEs (<0.001%) that were incorrectly coded. An additional 8 AEs were identified as possibly an incorrect interpretation of the investigator's intent, e.g., "hematoma of the left lower abdomen" coded as "abdominal hematoma" which subsequently becomes through the MedDRA dictionary "intra-abdominal hematoma." Incorrect or sub optimally coded AEs were spread across all arms and were not clustered within particular PT(s) or other MedDRA level, potentially affecting the overall safety assessment. Summaries of events for patients who died within 30 days of last dose of study treatment were reviewed for agreement with the Applicants assessment of cause. No discrepancies were identified.

Overall Exposure

Statistics for the duration of exposure to study treatment for Part 1 of COLUMBUS are shown in Table 48.

The median duration of exposure in the Combo 450 arm was 51.2 weeks (51.2 weeks for encorafenib and 50.6 weeks for binimetinib). This was longer than the median duration of exposure in the encorafenib monotherapy arm (31.4 weeks) and the vemurafenib arm (27.1 weeks). More than half of patients in the Combo 450 arm (52.6%) received at least 48 weeks of study treatment. Less than half of the patients in the encorafenib monotherapy arm (39.1%) and the vemurafenib arm (25.3%) received at least 45 weeks of study treatment. The median relative dose intensity in the Combo 450 arm was 100% for encorafenib and 99.6% for binimetinib. The median relative dose intensity in the encorafenib monotherapy arm was 86.2% and in the vemurafenib arm was 94.5%. Exposure time in the Combo ≥ 400 pool was shorter

than observed in the COLUMBUS Part 1 Combo 450 arm, with only 36% of patients receiving more than 48 weeks of treatment. The actual and mean dose intensity, however, was similar between the Combo 450 arm from COLUMBUS Part 1 and the pooled Combo ≥ 400 data.

Table 48: Duration of Exposure to Study Treatment: COLUMBUS Part 1 and Combo ≥ 400

	COLUMBUS Part 1					Combo ≥ 400 Pool		
	Combo 450							
Time on Treatment (weeks)	Encorafenib N=192	Binimetinib N=192	Encorafenib + Binimetinib N= 192	Enc 30 N= 192	Vem N=186	Encorafenib N=433	Binimetinib N=433	Encorafenib + Binimetinib N=433
Mean (SD)	54.29 (30.9)	53.77 (31.3)	54.32 (30.9)	42.4 (31.2)	35.9 (29.5)	41.9 (30.7)	41.6 (30.7)	42.0 (30.6)
Median	51.21	50.64	51.2	31.4	27.1	34.0	33.3	34.0
Range (min-max)	0.4 - 116.0	0.4 - 116.0	0.4 - 116.0	0.1 - 113.3	0.9 - 121.6	0.1-132.9	0.1-132.9	0.1-132.9
Exposure Category (weeks) n (%)								
< 12	13 (6.8)	15 (7.8)	13 (6.8)	29 (15.1)	35 (18.9)	67 (15.5)	68 (15.7)	66 (15.2)
12 to < 24	21 (10.9)	20 (10.4)	20 (10.4)	42 (21.9)	45 (24.2)	86 (19.9)	86 (19.9)	85 (19.6)
24 to < 36	32 (16.7)	32 (16.7)	33 (17.2)	32 (16.7)	38 (20.4)	71 (16.4)	71 (16.4)	72 (16.6)
36 to ≤ 48	25 (13.0)	25 (13.0)	25 (13.0)	14 (7.3)	21 (11.3)	52 (12.0)	53 (12.2)	53 (12.2)
≥ 48	101 (52.6)	100 (52.1)	101 (52.6)	75 (39.1)	47 (25.3)	157 (36.3)	155 (35.8)	157 (36.3)
Actual Dose Intensity (mg/day)								
Mean (SD)	410.3 (70.2)	79.8 (16.5)		227.0 (77.5)	1613.4 (372.5)	426.6 (75.3)	81.6 (14.8)	
Median	450.0	89.6		256.6	1814.13	450.0	89.4	
Min-Max	150.0-450.6	6.3-90.0		44.4-300.5	325.0-1920.0	100.0 - 900.0	6.3 – 180.0	
Relative Dose Intensity (%)								
Mean (SD)	91.2 (15.6)	88.7 (18.3)		75.7 (25.8)	84.0 (19.4)	91.2 (15.3)	90.6 (16.4)	
Median	100	99.6		86.2	94.49	99.4	99.4	
Min-Max	33.3 - 100.1	6.9 - 100		14.8 – 100.2	16.9 - 100	20.4-200.0	6.9-200	

Source: ISS Tables 1-11 and 1-12 submitted to application 6/30/2017. COLUMBUS Part 1 data verified by Reviewer using COLUMBUS Part 1 SDTM.ex

Relevant characteristics of the safety population:

Demographic information for all patients randomized on COLUMBUS is found in Table 24, Section 8.1.1. The removal of the 7 patients who did not receive any study treatment from the full analysis did not significantly change the assessment.

Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with the Combo 450 regimen, and the duration of treatment is adequate to allow assessment of adverse reactions over time. The safety database represents the gender, age, and race consistent with that observed in the overall population of patients who are diagnosed with melanoma. The size of the Combo ≥ 400 pool and the duration of treatment for those patients is adequate to assess incidence of rare events that may only occur in larger population.

COLUMBUS Part 1 randomized the Combo 450 treatment against encorafenib 300 monotherapy and against vemurafenib monotherapy. In the absence of a placebo arm, contribution of the underlying disease to adverse reactions cannot be assessed. Since patients in all arms received a BRAF inhibitor and patients in the Combo 450 arm received a higher dose of encorafenib than in the encorafenib monotherapy arm, the ability to assess the contribution of each agent, encorafenib or binimetinib, to the safety assessment is limited.

8.2.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission contained all required components of the eCTD. The overall quality and integrity of the application was adequate for substantive review to be completed.

Categorization of Adverse Event

AEs were reported by the Investigators in the CRF. All AEs reported for all trials contributing to pooled datasets including both the combination and monotherapy sets, were coded by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

For COLUMBUS, severity of AEs was coded by the Investigator according to NCI CTCAE V4.03 using Grade 1 to 4; CTCAE Grade 5 (death) was not to be used. All AEs and SAEs were collected after the main study informed consent was provided through 30 days after the last dose of study treatment. In addition, treatment-related SAEs were collected after 30 days. Progression of malignancy (including fatal outcome), if documented per RECIST, was not to be reported as an SAE. An abnormal laboratory value was recorded as an AE if considered by the Investigator to be clinically significant, induced clinical signs or symptoms, required concomitant therapy, or required change in study treatment. The Investigator AE reporting included an assessment of seriousness and relatedness along with action taken with the treatment. Treatment emergent AEs (TEAEs) were defined as an AE beginning between the day of the first exposure to study

drug(s) up to and including 30 days after the last dose of study drug(s). All trials contributing to pooled datasets followed similar guidelines for AE collection and any differences are assessed as not altering the overall analyses.

The COLUMBUS protocol defined an SAE as an AE that is fatal or life threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect, is medically significant, i.e., an event that jeopardizes the patient or may require medical or surgical intervention to prevent a serious event, or requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalizations for routine treatment or monitoring of study indication and not associated with deterioration in condition, for elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened, or social reasons/respite care in the absence of any deterioration on the patient's general condition are not considered SAEs.

The applicant performed an analysis based on ungrouped PT as well as standard MedDRA hierarchical groupings. The applicant also grouped PTs in their analysis of AEs of special interest (AESI) and their analysis of adverse drug reactions (ADRs). AESIs and ADRs are discussed in Section 8.2.4. This reviewer assessed the applicant's ADR groupings to adequately capture the reported adverse events in a clinically meaningful way and no additional safety signals were identified beyond those discussed below. The safety review presented here was performed on TEAEs regardless of Investigator's assessment of attribution.

Routine Clinical Assessments

For COLUMBUS, physical examinations, height and weight, performance status assessment, and vital signs were performed during screening (within 21 days of initiating study treatment), Day 1 of each cycle, at end of treatment (EOT), and at the 30-day safety follow-up visit. Vital signs included blood pressure, temperature, pulse, and respiratory rate measurements.

Routine laboratory assessments including hematology and clinical chemistries were performed during screening, Day 1 of each cycle, at EOT, and at 30-day safety follow up. Laboratory hematology assessments consisted of a complete blood count with platelets and differential. Routine clinical chemistry assessment consists of BUN/urea, uric acid, serum creatinine, sodium, potassium, magnesium, calcium, chloride, glucose, total protein, albumin, bicarbonate/CO2, phosphate, AST, ALT, GGT, alkaline phosphate, and bilirubin (direct, indirect, and total).

Cardiac/muscle enzyme studies consisting of troponin and creatine phosphokinase (CPK) were measured pre-dose during screening, Day 1 of each cycle, at EOT, and at 30-day safety follow up.

Additional Clinical Assessments

Ophthalmologic examinations including slit lamp examination, best recorded visual acuity for distance testing, intraocular pressure (IOP), and fundoscopy were required for all patients enrolled in COLUMBUS. Patients on the Combo 450 and Combo 300 arms as well as patients on the encorafenib monotherapy and vemurafenib arms with baseline retinal abnormalities were

required to have ophthalmic examinations during screening, at each regulatory scheduled patient visit (Day 1 of each cycle), EOT, and at the 30-day safety follow-up (per Amendment 3).

Standard 12-lead Electrocardiograms (ECGs) were performed during screening, Day 1 Cycles 1,2, and 3, every 3 cycles thereafter (every 12 weeks), EOT, and at the 30-day safety follow-up.

Cardiac imaging with multiple gated acquisition scan (MUGA) or echocardiography (ECHO) scan or echocardiograph (ECHO) was obtained during screening, Day 1 of Cycles 2 and 3, every 3 cycles thereafter (every 12 weeks), EOT, and at the 30-dat safety follow up visit.

Skin evaluations were performed for all patients on day 1 of odd cycles (every 8 weeks starting Day 1 Cycle 1), EOT, and at the 30-day safety follow-up visit.

8.2.3. Safety Results

Deaths

Table 49 summarizes the primary cause of death for patients in COLUMBUS Part 1 who died while on therapy or within 30 days of the last dose of treatment (treatment emergent deaths). Based on disposition data, at the time of cutoff (9 May 2016), there were 17 treatment emergent deaths in the Combo 450 arm, 14 deaths in the encorafenib monotherapy arm, and 19 deaths in the vemurafenib arm. Of these deaths, 11/17 (65%) on the Combo 450 arm were attributed to underlying disease while 12/14 (86%) on the encorafenib monotherapy arm and 17/19 (89%) on the vemurafenib arm were attributed to underlying disease. Three of 17 deaths (18%) on the Combo 450 arm, 1/14 deaths (7%) on the encorafenib monotherapy arm, and 2/19 (11%) were attributed to adverse events. The Applicant provided detailed narratives for all patients on COLUMBUS Trial who died within 30 days of last exposure of study drug. A review of these narratives was performed. Table 50 below summaries these narratives for patients in Part 1 where cause of treatment emergent death was assessed as other than disease progression.

Table 49: Primary Cause of Treatment Emergent Deaths: COLUMBUS Part 1

	COLUMBUS Part 1		
Primary Cause of Death	**Combo 450 N=192 n (%)**	**Enc 300 N=192 n (%)**	**Vem N=186 n (%)**
All deaths prior to cutoff	69 (35.9)	74 (38.5)	88 (47.3)
Deaths on therapy or within 30 days of treatment discontinuation	17 (8.9)	14 (7.3)	19 (10.2)
Reason for Death			
Study Indication[1]	11 (5.7)	12 (6.3)	17[2] (9.1)
Adverse Event	3 (1.6)	1 (1.0)	2 (1.1)
Acute Myocardial Infarction		1 (0.5)	
Cerebral Hemorrhage	1 (0.5)		
Suicide	1 (0.5)		

	COLUMBUS Part 1		
Primary Cause of Death	**Combo 450 N=192 n (%)**	**Enc 300 N=192 n (%)**	**Vem N=186 n (%)**
Intestinal Sepsis			1 (0.5)[3]
Lung Infection			1 (0.5)[4]
Multiple Organ Dysfunction Syndrome	1 (0.5)		
Other	3 (1.6)	1 (0.5)	
Euthanasia	1 (0.5)[5]		
Unknown	2 (1)	1 (0.5)	

Source: Reviewer generated table using COLUMBUS PART1: ADSL, (cutoff 9 May 2016, submitted by Applicant);
[1] Includes "malignant melanoma", "study indication", "metastases to CNS"
[2] Includes 1 patient for whom Investigator's assessment for cause of death was progressive disease, but upon review, cannot definitely be determined and 1 patient who died of "general physical health deterioration" who had no post-baseline tumor assessments but for whom the Investigator considered disease progression as a possible cause of death,
[3] Narrative notes patient also experienced Grade 5 pulmonary embolism concurrent with intestinal sepsis.
[4] Narrative also notes cause as disease progression (malignant pleural effusion).
[5] Narrative notes that prior to death, patient discontinued study treatment due to progressive disease, including hepatic metastases. Patient subsequently developed liver failure and reportedly opted for euthanasia.

Table 50: Summary of Applicant Narratives for Patients in COLUMBUS Part 1 Who Died ≤ 30 days of Treatment for Cause Other than Disease Progression

Patient	Treatment Arm	Reported Cause of death
(b) (6)	**Combo 450**	**Unknown cause**
The patient was a 51-year-old woman with a diagnosis of cutaneous melanoma, Stave IV M1c, with metastases to the bone, liver, lungs, skin, inguinal and other lymph nodes. Prior disease directed therapy included interferon. On study day 148, the patient died due to unknown reasons. The patient was found deceased at home with "no signs of suffering or vomiting, no rictus, no urine loss, and no missing drugs. No evidence of suicide was also noted." The patient was reported by her husband as well without complains in the days prior to death. Adverse events reported as ongoing at the time of death were fatigue (Grade 1), upper abdominal pain (Grade 1), dysgeusia (Grade 1), and headache (Grade 2) since day 86. The most recent AE was pain in the left armpit scar (Grade 1) noted on Day 112. Concomitant medications at the time of death included alprazolam, paroxetine hydrochloride, quetiapine fumurate and zopiclone, all initiated prior to randomization, as well as cathartics and acetaminophen. Patients most recent ECG on day 140 was normal and last LVEF measured on day 142 was 55% (52% at screening). Except for Troponin, which was mildly elevated at 12.0 ng/mL (ULN < 10 ng/mL), all laboratory results from Day 140 were within normal limits. This reviewer agrees with the Applicant's assessment that while a relationship between the event of death and the study drugs cannot be excluded, no clear relationship to study treatment is evident.		
(b) (6)	**Combo 450**	**Multiple organ dysfunction syndrome**
The patient was a 67-year-old gentleman with a diagnosis of cutaneous melanoma, Stage IV M1c with elevated LDH with metastases to the brain and axillary lymph nodes. Except for resection of brain metastasis, no prior disease directed therapy was reported. Relevant past medical conditions include atrial fibrillation. Active medical conditions at the time of randomization included hypertension and vertigo. On study Day 5, the patient was hospitalized with the SAE of epilepsy (Grade 3). On study Day 12, the patient experienced the SAE of pneumonia (Grade 3) and on study Day 14, the patient experienced the SAEs of gastric ulcer hemorrhage (Grade 2) and multiple organ dysfunction syndrome (Grade 4). No information on workup,		

including culture, lung imaging, or gastroscopy, was provided. Concomitant medications at the time of the event included losartan with hydrochlorothiazide, sotalol hydrochloride, and betahistine hydrochloride. The patient was treated with amoxicillin with clavulanic acid (Days 12-37) for the event of pneumonia and aminomethyl benzoic acid and etamsylate (Days 14-37) for the event of gastric hemorrhage. The study drugs were interrupted starting on Day 15. On day 37, 22 days after the last dose of study drug, the patient died due to gastric ulcer hemorrhage and multiple organ failure.

The Applicant agreed with the Investigator's assessment that there was no clear information to link death with study treatment. However, given the known association between hemorrhage and MEK inhibitors, in the absence of additional information, this reviewer concludes that the study drugs may have contributed to the cause of death, gastric hemorrhage, for this patient.

(b) (6)	**Vemurafenib**	**Disease Progression (Unknown)**

The patient was a 62-year-old gentleman with a diagnosis of cutaneous melanoma, Stave IV M1c with elevated LDH. Metastatic sites included lymph nodes, liver, spleen, lung, and adrenal gland. Prior disease directed therapy included lymphadenectomy and interferon. Relevant past medical conditions included cholecystectomy and thrombosis. The patient's active medical conditions at the time of randomization included anemia, hypertension, type 2 DM, and hyperlipidemia.

On study Day 57, the patient died. Abnormal laboratory results from study Day 28 included increased alkaline phosphatase (Grade 1, improving from baseline) and increased serum creatinine (Grade 1). LDH was WNL (elected at baseline). The last cardiac assessment performed on Day 32 showed a LVEF of 68% and normal ECG. There were no on-treatment tumor assessments.

The Investigator reported the cause of death as disease progression. The Applicant concluded that based on the patient's extensive disease burden and lack of evidence for alternative causes, disease progression as cause of death could not be excluded, the cause of death cannot be conclusively identified based on the information provided. This reviewer agrees with Applicant and would categorize cause of death as indeterminant.

(b) (6)	**Vemurafenib**	**Gastrointestinal sepsis**

The patient was a 48-year-old gentleman diagnosed with cutaneous melanoma, Stage IV M1c with normal LDH. Metastatic sites included lymph nodes, liver, and skin. No prior disease directed therapy was reported. Relevant active medical conditions at the time of randomization included anemia, lymphopenia, sarcoidosis, and renal failure.

On study Day 195, the patient experienced the SAE of increased GGT (Grade 4) and intestinal sepsis (Grade 4) and the non-serious AE of dyspnea (Grade 3). The patient was hospitalized with a gastrointestinal abscess and peritonitis complicated by septic shock. On Day 197, CT scan findings were consistent with right pulmonary embolism. The last day of study treatment was Day 195. On Day 206, 11 days after the last dose of study drug, the patient died due to the event of intestinal sepsis.

The Investigator suspected a relationship between the event of GGT increased and the study drug but did not suspect a relationship between the events of lymphopenia, intestinal sepsis, pulmonary embolism and the study drug. The Applicant agreed with the Investigator's assessment. This reviewer notes that the narrative grades the pulmonary embolism as fatal (Grade 5). This reviewer agrees with the Applicant's assessment regarding the relationship between intestinal sepsis and study treatment.

(b) (6)	**Combo 450**	**Cerebral hemorrhage**

The patient was a 54-year-old gentleman with a diagnosis of cutaneous melanoma, Stage IV M1c with normal LDH. Metastatic sites included extensive nodal disease, pleura, and lung. Prior disease directed therapy included excision of malignant lesions including lymphadenectomy. No prior antineoplastic medication or radiotherapy was reported. Relative active medical conditions at the time of randomization included hypertension (Grade 2 baseline).

On study Day 231, MRI of the brain performed for a complaint of headache showed metastases. Study drugs were permanently discontinued due to disease progression. Radiation therapy for brain metastases was started

on Day 235. On Day 237, 7 days after the last dose of study drugs, the patient experienced a non-serious event of brain edema (Grade 3) and the SAE of cerebral hemorrhage (Grade 3). On Day 240, CT scan showed progressive bleeding (acute bleeding into disseminated cerebral metastasis of melanoma) and edema. The patient died due to cerebral hemorrhage on Day 246, 16 days after the last dose of study drugs.

The Investigator did not suspect a relationship between the events of brain edema and cerebral hemorrhage and the study drugs. The Applicant did not assess a relationship. This reviewer agrees with the Investigator that the cerebral hemorrhage, the identified cause of death, was most likely due to confirmed disseminated cerebral metastasis of melanoma; however, given the known association between BRAF/MEK inhibitors and hemorrhage, a contributory affect of study treatment to the hemorrhage cannot be ruled out.

(b) (6)	**Combo 450**	**Unknown cause**

The patient is a 35-year-old gentleman with a diagnosis of cutaneous melanoma, Stave IV M1c with elevated LDH. Metastatic sites included lymph nodes, vertebra, liver, pleura, retroperitoneum, and spleen. Prior disease directed therapy included excision of skin lesion and interferon. No relevant medical conditions at the time of randomization were reported.

On Day 77, the patient died in Russia (out of the country) due to unknown reasons. The cause of death was not reported on the death certificate. No further information was reported despite information requests by the Investigator of the patient's relative. Non-serious adverse events that were ongoing at the time of death were anemia (Grade 3) and neutropenia (Grade 3). There were no reported laboratory assessments in the 2 weeks prior to the death. The most recent tumor assessment performed (Day 56) showed partial response.

The Investigator did not suspect a relationship between the event of death and the study drugs. The Applicant did not provide an assessment. This reviewer concludes there is insufficient information to assess the cause of death.

(b) (6)	**Encorafenib Monotherapy**	**Acute myocardial infarction**

The patient was a 54-year-old gentleman with a diagnosis of cutaneous melanoma, Stage IV M1c with elevated LDH. Metastatic sites included axillary lymph notes. Prior disease directed therapy included excision of melanoma on lower back. No prior antineoplastic medication or radiation was reported. Relevant active medical conditions at the time of randomization included muscular weakness and lymphedema.

On study Day 280, study drug was permanently discontinued due to disease progression. On Day 289, 9 days after the last dose of study drug, the patient experienced the serious adverse event of acute myocardial infarction. On Day 291, 11 days after the last dose of study drug, the patient died due to the event of acute myocardial infarction.

The Investigator did not suspect a relationship between the event of acute myocardial infarction and the study drug. The Applicant assessment was that the temporal relationship between the event and the study drug made a relationship with study drug improbable, citing the prolonged period on study drug preceding the event, and that the event of myocardial infarction occurred nearly 10 days after the last dose of study drug.

(b) (6)	**Vemurafenib**	**Disease progression (General health deterioration)**

The patient was a 68-year-old woman with a diagnosis of cutaneous melanoma, Stage IV M1c with normal LDH. Metastatic sites included bone, thoracic vertebrae, lymph nodes. No prior disease directed therapy was reported. The patient's relevant active medications at the time of randomization included atrial fibrillation, chronic obstructive pulmonary disease, diabetes mellitus, hemangioma of the liver, hypertension, and osteoporosis.

On study Day 28, the patient experienced the SAE of general physical health deterioration (Grade 4). No other AEs were reported and no laboratory results were provided. The patient did not have post-baseline tumor assessments. The patient received the last dose of study drug on Day 26. The patient is reported to have died due to the event of general physical heath deterioration.

The Investigator did not suspect a relationship between the event of general physical health deterioration and the study drug and considered disease progression as a possible cause. The Applicant agreed.

No post-baseline laboratory or cardiac assessments are available for the patient. Review of other patients treated at the same site demonstrates the Investigator regularly submitted AE reports for other patients suggesting the absence of other AEs for this patient likely accurately reflected the patient's condition. Based on the patient's multiple sites of disease at diagnosis and absence of other AEs reported, FDA agrees with the Applicant's assessment.

(b) (6)	**Vemurafenib**	**Disease progression/ Lung infection**

The patient was a 53-year-old gentleman with a diagnosis of cutaneous melanoma, Stage IV M1c with normal LDH. Metastatic sites included axillary lymph nodes and soft tissue. Prior disease directed therapy included radiation to axillary lymph nodes and right supraclavicular area. No prior antineoplastic medication was reported. The patient's relevant active medical conditions at the time of randomization included hypertension, lower extremity neuropathy, and type 2 diabetes mellitus.

On study Day 88. The patient was hospitalized due to a serious adverse event of pleural effusion (Grade 3) which was confirmed by CT scan. The pleural effusion was considered disease progression which was confirmed by the pathology report. On Day 89, the patient experienced a serious adverse event of lung infection (Grade 3). The patient was treated with penicillin. The patient underwent thoracostomies on Day 94 and Day 96. On Day 105, 16 days after the last dose of study drug, the patient died due to infection of the lung.

The Investigator did not suspect a relationship between the events of pleural effusion/ lung infection and the study drug. The patient's underlying disease was considered a possible contributory factor. The Applicant agreed with the Investigator's assessment. This reviewer agrees with the Applicant's assessment.

(b) (6)	**Encorafenib monotherapy**	**Unknown cause**

The patient is a 64-year-old woman with a diagnosis of cutaneous melanoma, Stage IV M1b. Metastatic sites included lung and soft tissue. Prior disease directed therapy included surgery (skin excisions and lymphadenectomy) and radiation (lymph node and skin). The patient's relevant medical conditions at the time of randomization included hypertension.

On study Day 377, the patient died due to unknown cause. No autopsy was performed. The last dose of study drug was taken on the same day. AEs at the time of death included keratoacanthoma (Grade 2), palmoplantar keratoderma (Grade 2), The last laboratory results including chemistry, hematology, and cardiac enzymes evaluated on Day 365 were within normal limits. The patient had stable disease at the time of the most recent prior tumor assessment on Day 345. The Investigator did not suspect a relationship between the event of death and the study drug. The Applicant assessed the death as not related to study drug and more likely related to the underlying disease of melanoma. This reviewer concludes there is insufficient information upon which to draw a conclusion.

(b) (6)	**Combo 450**	**Suicide**

The patient was a 73-year-old woman with a diagnosis of cutaneous melanoma, Stage IV M1a. Metastatic sites included skin. Prior disease directed therapy included excision of lesions including lymphadenectomy. No prior antineoplastic medication or radiation was reported. Relevant active medical conditions at the time of randomization included diabetes mellitus and hypercholesterolemia. The patient did not have reported previous psychiatric history.

On study Day 8, the patient reported nausea and vomiting for the prior 48 hours. On Day 9, the event of nausea was considered Grade 3. The study drug was discontinued on Day 9. On Day 10, the patient experienced the SAEs of fatigue (Grade 3), general physical health deterioration (Grade 3), hyperkalemia (Grade 3), renal failure (Grade 3), and vomiting (Grade 3). Concurrent non-serious events included somnolence (Grade 1). The patient additionally reported persistent nausea and vomiting, poor general condition, and persistent exhaustion. The patient was admitted to the hospital. Over the next several days, the patient's clinical condition improved. On Day 14, the patient reported feelings of depression with thoughts of hopelessness and death. According to the patient's family, the patient did not have symptoms of depression prior to the start of treatment with study drugs and was living an active life style, walking 5 km daily, and being responsible for her home and farm animals. The patient's family reported to have exhibited altered behavior due to depression since the beginning of treatment with study drugs. On Day 15, a psychological evaluation found the patient was alert and oriented without thought alterations although she did report apathy and weakness. No psychotic symptoms were observed and no psychopharmacological treatment was introduced. On Day 16, the patient was discharged from the hospital. At

the time, the patient did not report thoughts of suicide or death and had no nausea and vomiting. The event of general physical health deterioration was considered resolved now. On Day 22, the patient reported depressed mood and poor appetite. On Day 24, 15 days after the last dose of study drug, the patient fell from the 16th floor of a building and died. The Investigator suspected a relationship between the serious event of completed suicide and the study drugs. The Sponsor considered a causal relationship between study drug and the outcome of death by suicide possible. Given the significant change in the patient's activities and functioning that coincided with initiation of study treatment as well as a lack of prior psychiatric history, this reviewer agrees with the possible attribution of study drugs to this patient's death as a result of suicide.		
(b) (6)	**Combo 450**	**Euthanasia/ Liver failure**
The patient was a 43-year-old gentleman with a diagnosis of cutaneous melanoma, Stage IV M1c with normal LDH. Metastatic sites included bone, lumbar vertebrae, and lung. Prior disease directed therapy included surgical excision of melanoma metastasis right parieto-temporal, radiation therapy to the bone. No prior antineoplastic medication was reported. No active medical conditions at the time of randomization were reported. On Day 258, the patient received the last dose of study drugs due to disease progression, confirmed by PET scan on Day 258, which showed increased update in the liver and bone consistent with metastases. On Day 264, 8 days after the last dose of study drug, the patient experienced a non-serious adverse event of hepatic failure (Grade 3). On day 268, the patient died. The patient's death certificated noted hepatic failure. It is also reported the patient opted for euthanasia. The investigator did not suspect a relationship between the event of hepatic failure and study drugs. The Applicant agreed with the Investigator's assessment. This reviewer agrees with the Applicant's assessment.		

Source: Reviewer synopses of Applicant provided summaries COLUMBUS Part 1 CSR

Based on the completed suicide by Patient (b) (6), this clinical reviewer performed a more extensive evaluation of depression, including suicidal ideation and suicide attempts. A thorough examination of the ISS-ADAE datafile revealed a total of three AEs that referenced suicide (2 in addition to Patient (b) (6), whose history is summarized above).

- Patient (b) (6) is a 49-year-old male randomized to the COMBO 450 arm in COLUMBUS Part 1. The reported event Grade 4 "depression suicidal" occurred on day 337 of treatment and was reported as recovered/resolved on day 338. On Day 338, the AE of Grade 2 "depression" was reported. At the time of data cutoff, there was no AE end date to the AE depression. The patient's medical history did not include any psychiatric disorder. *Reviewer Comment: It seems unlikely if the suicidal ideation reported was related to treatment, that it would have resolved within 1 day.*

- A non-treatment emergent case of completed suicide occurred in Patient (b) (6), a 71-year-old male with a diagnosis of melanoma enrolled on CLGX818X2109 and receiving COMBO 450 therapy. Per the ADSL dataset, the patient was taken off study 30 days after initiating treatment due to progressive disease. He committed suicide 31 days after coming off therapy. There were no reports of depression while on therapy. *Reviewer Comment: While this event just misses being defined as treatment emergent, the patient's progressive disease and discontinuation from therapy provides a plausible inciting event for his suicide.*

Table 51 summarizes for COLUMBUS Part 1 and the pooled datasets (monotherapy and Combo ≥ 400) the incidence of patient past medical history (prior to enrollment) of psychiatric disorders and depression as well as the calculated incidence of psychiatric TEAEs at the SOC

level (Psychiatric Disorder) and two reviewer generated composite terms for depression and suicidal ideation and/or attempt. As seen in the table, a history of psychiatric disorder was common in all populations with patients in the encorafenib monotherapy arm of COLUMBUS Part 1 having a higher incidence. The incidence of a history of depression was similar across populations. In COLUMBUS Part 1, the incidence of depression based on a reviewer defined pool of PTs in the Combo 450 arm was similar to that observed in the encorafenib monotherapy arm while slightly higher than that observed in the vemurafenib arm. Across all arms and in the pooled populations, the incidence of depression on therapy is similar or better than the incidence of a past medical history of depression.

A total of 2 patients in the Combo 450 arm had Grade 3-4 depression. These events were the AEs related to suicide detailed above. There were no additional reports of Grade 3-4 treatment emergent depression or reports involving suicide or suicidal ideation in any population. The largest pool for combination therapy is the Combo ≥ 400 set which consists of 433 patients. In this population, the overall incidence of depression is 3.2 and the overall incidence of grade 3-4 depression as well as AEs associated with suicide is 0.005%.

In summary, while depression was a fairly common TEAE in COLUMBUS Part 1, as it is in cancer patients in general, it was rarely greater than Grade 2, and the incidence was not greater than the percentage of patients with a history of depression prior to enrollment. The most concerning reports are those related to suicide. A small number of suicides is not uncommon in large cancer clinical trials, even in patients without a history of depression. Overall, there were three reports of suicide or suicidality in the ISS database. One was not treatment emergent and is more adequately explained as related to progressive disease rather than study drugs. One case lasted for only 1 day, being replaced in the setting of continued therapy by Grade 2 depression without mention of suicidality. The third case of completed suicide by a patient with no history of depression while on therapy may be related to study treatment; however, on the basis of this single event, there is insufficient evidence to suggest that either encorafenib or binimetinib may pose a risk of life-threatening depression.

Table 51: Incidence of Past Medical History of Psychiatric Disorders and Treatment Emergent Psychiatric Disorders and Depression: COLUMBUS Part 1 and Pooled Datasets

	COLUMBUS Part 1			Pooled Data Sets		
	Combo 450 N=192	**Enc 300 N=192**	**Vem N=186**	**Combo ≥ 400 N=433**	**Bini 45 mg BID N=427**	**Enc 300 N=217**
H/O psychiatric disorder n(%)	31 (16.1)	51 (26.6)	33 (17.7)	103 (23.8)	75 (17.6)	56 (25.8)
H/O depression n(%)	12 (6.3)	13 (6.8)	15 (8.1)	36 (8.3)	32 (7.5)	16 (7.4)
TEAE Psychiatric disorder						
All Grade n (%)	42 (21.9)	64 (33.3)	31 (16.7)	76 (17.6)	45 (10.5)	78 (35.9)
Grade 3-4 n %)	3 (1.6)	6 (3.1)	0	7 (1.6)	3 (0.7)	8 (3.7)
TEAE Depression [1]						
All Grade n (%)	10 (5.2)	12 (6.3)	4 (2.1)	14 (3.2)	9 (2.1)	12 (5.5)
Grade 3-4 n (%)	2 (1.0)	0	0	2 (0.005)	0	0
TEAE Suicidal [2]	2 (1.0)	0	0	2 (0.005)	0	0

Source: Reviewer generated from ISS Table 1.4.2 (Relevant Medical Histories) and ISS:ADAE (submitted by Applicant)

[1] Reviewer generated composite term comprising the PTs: completed suicide, depressed mood, depression, depression suicidal, persistent depressive disorder.
[2] Reviewer generated composite term comprising the PTs: completed suicide, depression suicidal.

Serious Adverse Events

Table 52 summarizes SAEs for COLUMBUS Part 1. The proportion of patients experiencing at least one SAE was similar across all arms in COLUMBUS Part 1, with slightly higher incidence of any SAE, non-fatal SAE, fatal SAE, or Grade 3-4 SAE observed in the vemurafenib arm.

Table 52: Serious Treatment Emergent Adverse Events: COLUMBUS Part 1 and Pooled Combination Dataset

	COLUMBUS Part 1			Combo ≥ 400 Pool N=433 n (%)
	Combo 450 N= 192 n (%)	Enc 300 N= 192 n (%)	Vem N=186 n (%)	
Any SAE	66 (34.3)	65 (33.9)	69 (37.1)	158 (36.5)
Non-Fatal	60 (31.3)	58 (30.2)	66 (35.5)	147 (33.9)
Fatal[1]	9 (4.7)	6 (3.1)	10 (5.4)	16 (3.7)
Grade 3-4[2]	57 (29.7)	54 (28.1)	60 (32.3)	142 (32.8)

Source: generated from SDTM.AE, STDM.DM (COLUMBUS Part 1 cutoff 9 May 2016) and ISS_ADADR (Combo ≥400 Pool)
[1] Fatal SAEs are defined as those that resulted in death (AEDTH=Y) since Grade 5 was not to be used in COLUMBUS.
[2] May include SAEs that resulted in death

For COLUMBUS Part 1, there were 31 TEAEs with a fatal outcome reported in 25 patients (11 AEs in 9 patients in the Combo 450 arm, 11 AEs in 10 patients in the encorafenib monotherapy arm, and 9 AEs in 6 patients in the vemurafenib arm).

Table 53 summarizes TEAEs with an outcome of death that occurred within 30 days of receipt of study treatment and prior to cutoff date. Most notable is that 3 patients on the Combo 450 arm and 2 patients on the encorafenib monotherapy arm died as a result of cerebral hemorrhage, while no patients in the vemurafenib arm died as a result of cerebral hemorrhage. The event of cerebral hemorrhage was associated with brain metastases. While the difference may be the result of small numbers, it may also represent a greater risk of cerebral hemorrhage associated with encorafenib.

In the Combo ≥ 400 pool, there were 19 TEAEs with fatal outcome reported in 16 patients. Fatal events occurring in patients not included in

Table 53 included myocardial infarction (1 patient), brain edema (1 patient), sepsis (1 patient), rectal hemorrhage (1 patient), epileptic seizure and aphagia (1 patient).

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Table 53: Fatal Treatment Emergent Serious Adverse Events

	COLUMBUS Part 1		
	Combo 450 N=192 n (%)	**Enc 300 N=192 n (%)**	**Vem N=186 n (%)**
Patients with any AE with fatal outcome[1]	9 (4.6)	10 (5.2)	6 (3.1)
Cardiac disorders			
Acute myocardial infarction	0	1 (0.5)	0
Gastrointestinal disorders			
Abdominal pain upper	0	0	1 (0.5)
Ascites	0	0	1 (0.5)
Gastric ulcer hemorrhage	1 (0.5)	0	0
General disorders and administration site conditions			
Death	2 (1.0)	1 (0.5)	0
General physical health deterioration	1 (0.5)	0	2 (1.1)
Multi organ dysfunction syndrome	1 (0.5)	0	0
Non-cardiac chest pain	0	1 (0.5)	0
Metabolism and nutrition disorders			
Dehydration	0	0	1 (0.5)
Neoplasms benign, malignant and unspecified			
Metastases to central nervous system	0	3 (1.6)	0
Metastases to meninges	1 (0.5)	1 (0.5)	0
Nervous system disorders			
Brain stem syndrome	0	1 (0.5)	0
Cerebral hemorrhage	3 (1.6)	2 (1.0)	0
Coma	1 (0.5)	0	0
Hemiparesis	0	1 (0.5)	0
Nervous system disorder	0	0	1 (0.5)
Psychiatric disorders			
Suicide	1 (0.5)	0	0
Renal and urinary disorders			
Renal failure	0	0	1 (0.5)
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	0	0	1 (0.5)
Pulmonary embolism	0	0	1 (0.5)

Source: Reviewer generated table using COLUMBUS Part 1 ADAE (cutoff 9 May 2016, submitted Applicant)

[1] Based on reported outcome (AEDTH flag) and not AE toxicity grading

Table 54 shows the frequency of SAEs by PT (occurring in at least 2 patients (≥1 %) in the Combo 450 arm). Only the following terms occurred in more than 2% of patients in the Combo 450 arm: pyrexia (3.1%), anemia (2.1%), and abdominal pain (2.1%).

At the MedDRA higher level term (HLT) groupings, only the following terms occurred in more than 2% of patients in the Combo 450 arm: gastrointestinal disorders (3.1%), febrile disorders

(3.1), renal failure and impairment (2.6%), general signs and symptoms NEC (2.1%), nausea and vomiting symptoms (2.1%), and anemias NEC (2.1%).

At the MedDRA level of higher level group term (HLGT) only the following terms occurred in more than 2% of patients in the Combo 450 arm: infections – pathogen unspecified (6.3%), general system disorder NEC (4.7%), gastrointestinal signs and symptoms (4.7%), Neurological disorders NEC (3.1%), body temperature conditions (3.1%), renal disorders - excl nephropathies (2.6%), bacterial infectious disorders (2.6%), central nervous system vascular disorders (2.6%), and anemias nonhemolytic and marrow depression (2.1%).

The incidence of SAEs by the MedDRA Grouping SOC is shown in Table 55. At this level, only the following terms occurred in more than 5% of patients in the Combo 450 arm: gastrointestinal disorders (9.4%), infections and infestations (8.9%), general disorders and administration site conditions (8.3%) and nervous system disorders (7.3). For these terms, the incidence is higher in the Combo 450 arm than in the vemurafenib arm. Drilling down in the SOC nervous system disorders, the PTs occurring most often in the Combo 450 arm (≥ 2 patients) were: cerebral hemorrhage (3), balance disorder (2), dizziness (2), and transient ischemic attack (2). As noted previously, cerebral hemorrhage occurred in a slightly higher proportion of patients in the Combo 450 arm (1.5%) than in the vemurafenib arm (0.5%). No patients in the vemurafenib experienced balanced disorder or dizziness or transient ischemic attack.

Analysis of the Combo ≥ 400 pooled dataset did not identify any new SAEs of interest. At the PT level, the following SAEs occurred in ≥ 1 % of patients: vomiting (3.9%), nausea (3.5%), pyrexia (3.5%), abdominal pain (1.8%), anemia (1.8%), general physical health deterioration (1.8%), pneumonia, (1.6%), and diarrhea (1.4%). At the HLT level, the following groups occurred in ≥ 2 % of patients: nausea and vomiting symptoms (4.8%), febrile disorders (3.5%), gastrointestinal and abdominal pains (2.3%), and general signs and symptoms NEC (2.1%). At the HLGT level, the following groups occurred in ≥ 2% of patients: gastrointestinal signs and symptoms (6.7%), infections – pathogen unspecified (5.3%), general system disorders NEC (4.6%), body temperature conditions (3.5%), and bacterial infectious disorders (2.1%). Incidence at the SOC level is included in Table 55. The incidence between the Combo 450 arm in the COLUMBUS trial and the pooled Combo ≥ 400 dataset are remarkably similar for both all grades and Grade 3-4 events at the SOC level.

Table 54: SAEs Occurring in at Least 2 patients (≥ 1%) in the Combo 450 Arm: COLUMBUS Part 1

	COLUMBUS Part 1		
Preferred Term	**Combo 450 N=192 n (%)**	**Enc 300 N=192 n (%)**	**Vem N=186 n (%)**
Pyrexia	6 (3.1)	3 (1.6)	2 (1.1)
Anemia	4 (2.1)	1 (0.5)	2 (1.1)
Abdominal pain	4 (2.1)	2 (1.0)	1 (0.5)
General physical health deterioration	3 (1.6)	2 (1.0)	6 (3.2)
Pulmonary embolism	3 (1.6)	0	2 (1.1)
Vomiting	3 (1.6)	6 (3.1)	2 (1.1)
Acute kidney injury	3 (1.6)	1 (0.5)	1 (0.5)
Cerebral hemorrhage	3 (1.6)	2 (1.0)	1 (0.5)
Pneumonia	3 (1.6)	0	0
Pleural effusion	2 (1.0)	1 (0.5)	2 (1.1)
Abdominal pain upper	2 (1.0)	2 (1.0)	1 (0.5)
Death	2 (1.0)	1 (0.5)	0
Erysipelas	2 (1.0)	1 (0.5)	0
Nausea	2 (1.0)	6 (3.1)	0
Non-cardiac chest pain	2 (1.0)	2 (1.0)	0
Balance disorder	2 (1.0)	0	0
Cellulitis	2 (1.0)	0	0
Colitis	2 (1.0)	0	0
Dizziness	2 (1.0)	0	0
Myocardial infarction	2 (1.0)	0	0
Transient ischemic attack	2 (1.0)	0	0
Urinary tract infection	2 (1.0)	0	0

Source: Reviewer generated table using COLUMBUS Part 1 ADAE (cutoff 9 May 2016, submitted Applicant)

Table 55: Incidence of Serious Adverse Event All Grades and Grades 3-4 by SOC: COLUMBUS Part 1 and Combo ≥400 Pool

	COLUMBUS Part 1						Combo ≥ 400 Pool N=433 n (%)	
	Combo 450 N=192 n (%)		Enc 300 N=192 n (%)		Vem N=186 n (%)			
SOC	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Gastrointestinal disorders	18 (9.4)	15 (7.8)	15 (7.8)	13 (6.8)	10 (5.4)	9 (4.8)	52 (12.0)	43 (9.9)
Infections and infestations	17 (8.9)	16 (8.3)	5 (2.6)	4 (2.1)	9 (4.8)	7 (3.8)	32 (7.4)	28 (6.5)
General disorders and administration site conditions	16 (8.3)	14 (7.3)	13 (6.8)	12 (6.3)	11 (5.9)	8 (4.3)	34 (7.9)	27 (6.2)
Nervous system disorders	14 (7.3)	12 (6.3)	13 (6.8)	8 (4.2)	12 (6.5)	9 (4.8)	27 (6.2)	24 (5.5)
Respiratory, thoracic and mediastinal disorders	8 (4.2)	7 (3.6)	5 (2.6)	5 (2.6)	9 (4.8)	7 (3.8)	15 (3.5)	12 (2.8)
Renal and urinary disorders	6 (3.1)	4 (2.1)	3 (1.6)	3 (1.6)	6 (3.2)	5 (2.7)	10 (2.3)	8 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (2.6)	5 (2.6)	11 (5.7)	9 (4.7)	12 (6.5)	11 (5.9)	11 (2.5)	11 (2.5)
Blood and lymphatic system disorders	4 (2.1)	4 (2.1)	1 (0.5)	1 (0.5)	3 (1.6)	2 (1.1)	10 (2.3)	9 (2.1)
Cardiac disorders	4 (2.1)	2 (1.0)	4 (2.1)	2 (1.0)	4 (2.2)	3 (1.6)	8 (1.8)	6 (1.4)
Musculoskeletal and connective tissue disorders	4 (2.1)	3 (1.6)	13 (6.8)	11 (5.7)	8 (4.3)	6 (3.2)	10 (2.3)	8 (1.8)
Psychiatric disorders	3 (1.6)	3 (1.6)	0	0	1 (0.5)	0	5 (1.2)	5 (1.2)
Vascular disorders	3 (1.6)	1 (0.5)	0	0	0	0	5 (1.2)	3 (0.7)
Eye disorders	2 (1.0)	1 (0.5)	2 (1.0)	1 (0.5)	1 (0.5)	0	6 (1.4)	5 (1.2)
Injury, poisoning and procedural complications	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.1)	2 (1.1)	6 (1.4)	4 (0.9)
Metabolism and nutrition disorders	2 (1.0)	2 (1.0)	4 (2.1)	4 (2.1)	5 (2.7)	4 (2.2)	10 (2.3)	9 (2.1)
Skin and subcutaneous tissue disorders	2 (1.0)	1 (0.5)	2 (1.0)	1 (0.5)	9 (4.8)	8 (4.3)	4 (0.9)	3 (0.7)
Hepatobiliary disorders	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.5)
Investigations	1 (0.5)	0	3 (1.6)	2 (1.0)0	5 (2.7)	2 (1.1)	8 (1.8)	7 (1.6)
Congenital, familial and genetic disorders	0	0	1 (0.5)	1 (0.5)	0	0	0	0
Immune system disorders	0	0	1 (0.5)	1 (0.5)	2 (1.1)	1 (0.5)	0	0
Product issues	0	0	1 (0.5)	1 (0.5)	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	1 (0.5)	1 (0.5)	0	0

Source: Reviewer generated table using COLUMBUS Part 1 SDTM.AE (cutoff 9 May 2016, submitted Applicant) and ISS_ADAE (submitted by Applicant)

Dropouts and/or Discontinuations Due to Adverse Effects

With sponsor's approval, patients were allowed to continue on study drug beyond locally determined disease progression confirmed by the BIRC. Of the 50 total on-treatment deaths, 8 patients were treated ≥ 30 days beyond progression per the BIRC (3 patients on the Combo 450 arm, 2 patients on the encorafenib monotherapy arm, 3 patients on the vemurafenib arm).

Table 56 summarizes study discontinuations for COLUMBUS Part 1 and the Combo ≥ 400 Pooled dataset. Based on information provided in the disposition dataset, as of Part 1 data cutoff, treatment was ongoing for 24.7% of patients across arms. A higher percentage of patients in the Combo 450 arm were ongoing (35.4%) compared to patients in the encorafenib monotherapy (24.0%) and vemurafenib (14.5%) arms. The most common reason for discontinuation from study treatment in all arms was progressive disease. The percentage of discontinuation due to progressive disease was higher in the vemurafenib arm compared to either of the other two arms in Part 1. A smaller percentage of patients discontinued treatment due to adverse events in the Combo 450 arm than in either of the two other arms in Part 1.

Further examination of discontinuations due to "Physician Decision" and "Subject/Guardian Decision" identified 23 additional discontinuations due to disease progression (7 in the Combo 450 arm, 10 in the encorafenib arm, 6 in the vemurafenib arm) and 13 additional discontinuations due to toxicities (2 in the Combo 450 arm, 8 in the encorafenib arm, and 3 in the vemurafenib arm). These additional cases are grouped under "Reviewer's grouped reason for discontinuation" with progressive disease or toxicity, also shown in Table 56 for COLUMBUS Part 1 only. This information did not change the overall conclusion that a smaller percentage of patients in the Combo 450 arm discontinued treatment due to progressive disease or toxicity. The larger pooled dataset shows a pattern of discontinuations similar to that observed in the Combo 450 arm. Disposition in the Combo ≥ 400 pooled dataset and primary reason for discontinuation were similar to what was observed in the COLUMBUS Combo 450 arm.

Table 56: Discontinuations prior to cutoff by Investigator and Reviewer Assessed Reason: COLUMBUS Part 1 and Combo ≥ 400 Pool

	COLUMBUS Part 1			Combo ≥ 400 Pool N=433 n (%)
	Combo 450 N= 192 n (%)	Enc 300 N= 192 n (%)	Vem N=186 n (%)	
Treatment Ongoing at Cutoff date	68 (35.4)	46 (24.0)	27 (14.5)	149 (34.4)
Treatment Discontinued	124 (64.6)	146 (76.0)	159 (85.5)	284 (65.6)
Primary reason for discontinuation				
Adverse Event	16 (8.3)	24 (12.5)	26 (14)	31 (7.2)
Completed	0	0	0	4 (0.9)
Death	7 (3.6)	1 (0.5)	4 (2.2)	21 (4.8)
Lost to Follow-Up	1 (0.5)	1 (0.5)	0	1 (0.2)
Physician Decision	8 (4.2)	19 (9.9)	13 (7)	16 (3.7)
Progressive Disease	83 (43.2)	87 (45.3)	101 (54.3)	194 (44.8)

	COLUMBUS Part 1			Combo ≥ 400 Pool N=433 n (%)
	Combo 450 N= 192 n (%)	Enc 300 N= 192 n (%)	Vem N=186 n (%)	
Protocol Deviation	2 (1)	1 (0.5)	0	3 (0.7)
Withdrawn by Subject/Guardian	7 (3.6)	13 (6.8)	15 (8.1)	14 (3.2)
Reviewer Grouped Reason for Discontinuation				
Death	7 (3.6)	1 (0.5)	4 (2.2)	
Progressive Disease	90 (46.9)	98 (51.0)	107 (57.5)	
Toxicity	18 (9.4)	32 (16.7)	29 (15.6)	
Pursue other treatments	0	4 (2)	5 (2.7)	

Source: Reviewer generated table using COLUMBUS Part 1 SDTM.DS (cutoff 9 May 2016, submitted Applicant) and Combo ≥400 data from ISS Table 1-17

Based on the reported adverse event data, across all arms in COLUMBUS Part 1, 14% of patients (82/570) had an adverse event that led to permanent discontinuation of study treatment. The percentage of patients in the Combo 450 arm (12.5%) was lower than that observed in the encorafenib monotherapy arm (14.0%) and the vemurafenib arm (16.1%). The following AEs, by PT, led to discontinuation in at least 2 patients (≥1%) on the Combo 450 arm: alanine aminotransferase increased (2.6%), aspartate aminotransferase increased (2.6%), blood creatinine increased (1.0%), gamma-glutamyl transferase increased (1.0%), and headache (1.0%). These AEs occurred in a total of 8 patients. The AEs leading to discontinuation in ≥1% of patients in the Combo 450 arm were alanine aminotransferase increased (1.6%), aspartate aminotransferase increased (1.6%), blood creatinine increased (1.2%).

Table 57 summarizes at the SOC level TEAEs that led to discontinuation in at least 2 patients in the Combo 450 arm. Analysis at the SOC level of AEs leading to discontinuation shows results similar to those observed in the Combo 450 arm of COLUMBUS. No SOC group not shown in the table occurred in ≥ 1% of patients in the Combo ≥ 400 pool.

Table 57: TEAEs at the SOC Level Leading to Discontinuation ≥ 1% of patients in Combo 450 arm: COLUMBUS Part 1 and Combo ≥400 Pool

AESOC	Combo 450 N=192 n (%)	Enc 300 N=192 n (%)	Vem N=186 n (%)	Combo ≥ 400 Pool N=433 n (%)
Investigations	7 (3.6)	4 (2.1)	5 (2.7)	15 (3.5)
General disorders and administration site conditions	4 (2.1)	1 (0.5)	2 (1.1)	6 (1.4)
Gastrointestinal disorders	3 (1.6)	5 (2.6)	9 (4.8)	7 (1.6)
Neoplasms benign, malignant and unspecified	3 (1.6)	4 (2.1)	1 (0.5)	3 (0.7)
Nervous system disorders	3 (1.6)	4 (2.1)	3 (1.6)	6 (1.4)
Infections and infestations	2 (1.0)	0	1 (0.5)	2 (0.5)

Source: Reviewer generated table using COLUMBUS Part 1 SDTM.AE (cutoff 9 May 2016, submitted Applicant) and ISS_ADADR (Combo ≥400 pool)

Dose Interruptions and Reductions

Table 58 summarizes the frequency of adverse events leading to dose interruptions and reductions for COLUMBUS Part 1 and the Combo ≥ 400 pooled dataset. Across COLUMBUS Part 1 arms, 59.8% of patients had an adverse event that led to temporary interruption and/or dose reduction of study treatment. The percentage of patients in whom an AE led to dose interruption and/or reduction was lower in the Combo 450 arm (48%) than in the encorafenib monotherapy (70%) and the vemurafenib (61%) arms. This was also true for AEs leading to dose interruptions and to dose reductions when considered separately.

The specific AEs at the PT level that led to dose interruption and/or reduction in at least ≥ 2% of patients in the Combo 450 arm are summarized in Table 59. The most common PT leading to dose interruption and/or reduction in at least 5% of patients are: nausea (8%), vomiting (7%) and ejection fraction decreased (5%). The proportion of patients with nausea leading to dose interruption and/or reduction was similar across arms in Part 1; however, the proportion of patients with vomiting leading to dose interruption and/or reduction was higher in the Combo 450 arm and the encorafenib monotherapy arm when compared to the vemurafenib arm. The AE of ejection fraction decreased leading to dose interruption and/or reduction was only observed in the Combo 450 arm.

In the Combo ≥400 pool, the most common AEs leading to dose interruption/reduction in ≥2% of patients were ALT increased (5.3%), AST increased (4.4%), nausea (4.4%), lipase increased (3.2%), diarrhea (2.8%), vomiting (2.8%), GGT increased (2.5%), ejection fraction decreased (2.3%), pyrexia (2.3%), amylase increased (2.1%), and blood creatine phosphokinase increased (2.1%). These AEs are also seen in the list of AEs that lead to interruption/reduction in the Combo 450 arm of COLUMBUS. No new AEs that lead to dose reduction/interruption in ≥ 2% of patients is identified in the Combo ≥ 400 pool.

Table 58: Frequency of Adverse Events leading to Dose interruptions/reductions: COLUMBUS Part 1

	COLUMBUS Part 1			Combo ≥ 400 Pool N=433 n (%)[1]
	C_450 N=192 n (%)	Enc 300 N=192 n (%)	Vem N=186 n (%)	
AE leading to dose interrupted	88 (45.8)	122 (63.5)	98 (53.7)	
Grade 3-4	62 (32.3)	77 (40.1)	64 (34.4)	
AE leading to dose reduction	22 (11.5)	52 (27.0)	42 (22.6)	
Grade 3-4	4 (2.1)	17 (8.9)	10 (5.4)	
AE leading to dose interruption or reduction	92 (47.9)	135 (70.3)	114 (61.3)	212 (49.0)
Grade 3-4	63 (32.8)	85 (44.3)	71 (38.2)	141 (32.6)

Source: Reviewer generated table using COLUMBUS Part 1 SDTM.AE (cutoff 9 May 2016, submitted Applicant) and ISS_ADADR (Combo ≥400 pool)

[1] Because of how some studies were coded, action taken in response to an AE, i.e., interruptions and reductions cannot be tabulated separately

Table 59: TEAEs by PT leading to dose interruption and/or dose reduction in ≥ 2% of patients in Combo 450 arm: COLUMBUS Part 1

	COLUMBUS Part 1		
PT	**Combo 450 N=192 n (%)**	**Enc 300 N=192 n (%)**	**Vem N=186 n (%)**
Nausea	16 (8.3)	17 (8.9)	14 (7.5)
Vomiting	13 (6.8)	10 (5.2)	4 (2.2)
Ejection fraction decreased	10 (5.2)	0	0
GGT increased	9 (4.7)	4 (2.1)	2 (1.1)
Pyrexia	8 (4.2)	5 (2.6)	14 (7.5)
ALT increased	7 (3.6)	4 (2.1)	4 (2.2)
Diarrhea	7 (3.6)	4 (2.1)	9 (4.8)
AST increased	6 (3.1)	2 (1.0)	3 (1.6)
Blood CPK	6 (3.1)	0	1(0.5)
Abdominal pain	5 (2.6)	3 (1.6)	2 (1.1)
Anemia	4 (2.1)	2 (1.0)	2 (1.1)
Arthralgia	4 (2.1)	24 (12.5)	16 (8.6)
Blood ALP	4 (2.1)	1 (0.5)	1 (0.5)
Blood creatinine increased	4 (2.1)	0	4(2.2)
Dizziness	4 (2.1)	0	0
Fatigue	4 (2.1)	4 (2.1)	7 (3.8)
Hyperkeratosis	4 (2.1)	10 (5.2)	2 (1.1)
Hypertension	4 (2.1)	1 (0.5)	2 (1.1)
Retinal detachment	4 (2.1)	1 (0.5)	1(0.5)

Source: Reviewer generated table using COLUMBUS Part 1 SDTM.AE (cutoff 9 May 2016, submitted by Applicant)
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase.

Significant Adverse Events

The ICH E3 guidance recommends that marked laboratory abnormalities not meeting the definition of SAEs also be considered significant AEs. Laboratory findings are discussed in a separate section below. In addition, the ICH E3 guidance considers other potentially important abnormalities, such as severe AEs (i.e., ≥ Grade 3 by CTCAE) that do not meet the definition of a serious AE as potentially significant.

Table 60 shows the incidence of Grade 3-4 TEAEs by PT occurring in ≥ 1 % of patient in the Combo 450 arm for COLUMBUS Part 1 arms. PTs which are not previously identified as SAEs occurring in at least 1% of patients in the Combo 450 arm (Table 54) are noted in bold. The only two AEs at the PT level that occur at Grade 3-4 severity in ≥ 1% of patients in the Combo ≥400 pool that does not also occur in ≥ 1% of patients in the Combo 450 arm of COLUMBUS are

hyponatremia which occurs in 1.6% of patients and arthralgia which occurred in 1.2% of patients in the Combo > 400 pool.

The incidence of Grade 3-4 TEAEs by SOC occurring in at least 2 patients (1%) in the Combo 450 arm, are shown in Table 61 for COLUMBUS Part 1. Analysis of the incidence of Grade 3-4 TEAEs at the SOC level in the Combo ≥400 pooled did not identify any SOC group occurring in ≥1% of patients not identified in the Combo 450 arm of COLUMBUS (Table 61).

Table 60: Incidence GRADE 3 and 4 TEAEs occurring in ≥ 1% of Patients in Combo 450 arm: COLUMBUS Part 1

	COLUMBUS Part 1		
PT	**Combo 450 N=192 n (%)**	**Enc 300 N=192 n (%)**	**Vem N=186 n (%)**
GGT increased	18 (9.4)	9 (4.7)	6 (3.2)
Blood CPK increased	13 (6.8)	0	0
Hypertension	11 (5.8)	6 (3.1)	6 (3.2)
ALT	10 (5.2)	2 (1)	3 (1.6)
Anemia	8 (4.2)	5 (2.6)	4 (2.2)
Pyrexia	7 (3.6)	2 (1.0)	0
Abdominal pain	5 (2.6)	4 (2.1)	1 (0.5)
Diarrhea	5 (2.6)	3 (1.6)	4 (2.2)
AST increased	4 (2.1)	1 (0.5)	3 (1.6)
Fatigue	4 (2.1)	1 (0.5)	4 (2.2)
Pleural effusion	4 (2.1)	2 (1.0)	1 (0.5)
Hyperglycemia	4 (2.1)	4 (2.1)	0
Abdominal pain upper	2 (1.0)	2 (1.0)	1 (0.5)
Acute kidney injury	2 (1.0)	1 (0.5)	1 (0.5)
Amylase increased	3 (1.6)	0	2 (1.1)
Asthenia	3 (1.6)	5 (2.6)	8 (4.3)
Cerebral hemorrhage	3 (1.6)	2 (1.0)	1 (0.5)
Dizziness	3 (1.6)	0	0
General physical health deterioration	3 (1.6)	3 (1.6)	8 (4.3)
Headache	3 (1.6)	6 (3.1)	1 (0.5)
Lipase increased	3 (1.6)	2 (1.0)	2 (1.1)
Nausea	3 (1.6)	8 (4.2)	3 (1.6)
Pneumonia	3 (1.6)	1 (0.5)	0
Vomiting	3 (1.6)	9 (4.7)	2 (1.1)
Balance disorder	2 (1.0)	0	0
Blood creatinine increased	2 (1.0)	0	1 (0.5)
Cellulitis	2 (1.0)	0	0
Cholestasis	2 (1.0)	1 (0.5)	0
Chorioretinopathy	2 (1.0)	0	0

	COLUMBUS Part 1		
PT	**Combo 450 N=192 n (%)**	**Enc 300 N=192 n (%)**	**Vem N=186 n (%)**
Colitis	2 (1.0)	0	0
Death	2 (1.0)	1 (0.5)	0
Diverticulitis	2 (1.0)	0	0
Ejection fraction decreased	2 (1.0)	2 (1.0)	0
Erysipelas	2 (1.0)	1 (0.5)	0
Gastroenteritis	2 (1.0)	1 (0.5)	1 (0.5)
Hyperkaliemia	2 (1.0)	1 (0.5)	0
Hypophosphatasemia	2 (1.0)	0	2 (1.1)
Neutropenia	2 (1.0)	1 (0.5)	1 (0.5)
Non-cardiac chest pain	2 (1.0)	3 (1.6)	1 (0.5)
Edema peripheral	2 (1.0)	0	1 (0.5)
Pain in extremity	2 (1.0)	2 (1.0)	2 (1.1)
Pulmonary embolism	2 (1.0)	1 (0.5)	1 (0.5)
Rash	2 (1.0)	4 (2.1)	6 (3.2)
Renal failure	2 (1.0)	2 (1.0)	1 (0.5)
Urinary tract infection	2 (1.0)	0	0
Weight increased	2 (1.0)	0	0

Source: Reviewer generated table using COLUMBUS Part 1 SDTM.AE (cutoff 9 May 2016, submitted by Applicant)
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase.

Table 61: INCIDENCE OF GRADE 3 and 4 TEAEs by SOC occurring in >= 1% of Patients in Combo 450 arm: COLUMBUS Part 1

	COLUMBUS Part 1		
SOC	**Combo 450 N=192 n (%)**	**Enc 300 N=192 n (%)**	**Vem N=1862 n (%)**
Investigations	47 (24.5)	17 (8.9)	14 (7.5)
General disorders and administration site conditions	24 (12.5)	21 (10.9)	24 (13.0)
Gastrointestinal disorders	22 (11.5)	25 (13.0)	19 (10.2)
Infections and infestations	19 (10.0)	6 (3.1)	9 (4.8)
Nervous system disorders	18 (9.4)	18 (9.4)	14 (7.5)
Vascular disorders	12 (6.3)	7 (3.7)	6 (3.2)
Blood and lymphatic system disorders	11 (5.7)	9 (4.7)	9 (4.8)
Metabolism and nutrition disorders	10 (5.2)	14 (7.3)	10 (5.4)
Respiratory, thoracic and mediastinal disorders	8 (4.2)	10 (5.2)	8 (4.3)
Skin and subcutaneous tissue disorders	6 (3.1)	43 (22.4)	38 (20.4

SOC	COLUMBUS Part 1		
	Combo 450 N=192 n (%)	Enc 300 N=192 n (%)	Vem N=1862 n (%)
Eye disorders	5 (2.6)	1 (0.5)	1 (0.5)
Musculoskeletal and connective tissue disorders	5 (2.6)	43 (22.4)	19 (10.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (2.6)	11 (5.7)	22 (11.8)
Renal and urinary disorders	5 (2.6)	4 (2.1)	6 (3.2)
Hepatobiliary disorders	4 (2.1)	1 (0.5)	2 (1.1)
Psychiatric disorders	3 (1.6)	6 (3.1)	0
Cardiac disorders	2 (1.0)	4 (2.1)	5 (2.7)
Injury, poisoning and procedural complications	2 (1.0)	3 (1.6)	4 (2.2)

Source: Reviewer generated table using COLUMBUS Part 1 SDTM.AE (cutoff 9 May 2016, submitted by Applicant)

Treatment Emergent Adverse Events

The most commonly occurring TEAEs for the Combo 450 arm (≥ 10 % all grades, ≥ 2 % Grade 3-4) by PT are shown in Table 62. The following common TEAEs were not identified in previous analyses of serious and significant AEs: arthralgia, headache, constipation, asthenia, vision blurred, rash, hypertension, ALT increased, and edema peripheral. These PTs in general represent common but rarely serious or significant adverse events.

Comparing the frequency of TEAEs in the Combo ≥ 400 pool dataset with the frequency in the Combo 450 arm reveals identified the single AE retinopathy as occurring in ≥10% of patients in the Combo ≥ 400 pool but < 10% in the Combo 450 arm and where the difference in frequency between the two datasets is ≥ 5%. The frequency of retinopathy in the Combo 450 arm is 2.1% and in the Combo ≥400 pool is 10.6%. This represents a common event that is likely under-reported in the Combo 450 arm.

Comparing the Grade 3-4 TEAEs in the Combo ≥400 pool dataset with the frequency in the Combo 450 arm, two AEs, not previously identified in Table 62 have a frequency ≥ 2% in the Combo ≥ 400 pool but ≤ 2% in the Combo 450 arm: lipase increased and amylase increased. These are more adequately evaluated with laboratory assessments.

TEAEs occurring in ≥1% of patients in the Combo ≥400 pool but in ≤ 1% of patients in the Combo 450 arm included: detachment of reginal pigment epithelium (RPED) (Combo 450 arm: 0%, Combo ≥400: 2.8%), hypocalcemia (Combo 450 arm: 0%, Combo ≥400 pool: 1.8%), hypokalemia (Combo 450 arm: 0.5%, Combo ≥400 pool: 1.8%), and electrocardiogram QT prolongation (Combo 450 arm: 0%, Combo ≥400 pool: 1.2%). These AEs represent rare but potentially serious events that are only observed in the larger pooled dataset. Hypokalemia, hypocalcemia, and QT prolongation are discussed with laboratory assessments and ECG monitoring later in this section of the review. RPED is a known toxicity associated with MEK inhibitors and is discussed further in Section 8.2.4.

Table 63 presents the incidence of TEAEs at the SOC level for COLUMBUS Part 1. The following SOC terms occur more frequently (≥ 5% increase) in the Combo 450 arm when compared to the vemurafenib arm (% increase): eye disorders (+21%), investigations (+12%), nervous system disorders (+8%), and psychiatric disorders (+5%). The following SOC terms occurred less frequently (≥ 5% decrease) in the Combo 450 arm when compared to the vemurafenib arm (% decrease): skin and subcutaneous tissue disorders (-26%), general disorders and administration site conditions (-6%), musculoskeletal and connective tissue disorders (-14%), and neoplasms benign, malignant and unspecified (-21%). These differences most likely represent the effect of adding the MEK inhibitor to a BRAF inhibitor. Analysis of TEAEs at the MedDRA levels Higher Level Term (HLT), Higher Level Group Term (HLGT) did not identify additional any safety signals.

Table 62: TEAE Occurring in ≥ 10% All Grades or ≥ 2 % Grade 3-4 in Combo 450 Arm: COLUMBUS Part 1

	COLUMBUS Part 1					
	Combo 450 N=192 n (%)		Enc 300 N=192 n (%)		Vem N=1862 n (%)	
Preferred Term	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Nausea	79 (41.2)	3 (1.6)	74 (38.5)	8 (4.2)	63 (33.9)	3 (1.6)
Diarrhea	70 (36.5)	5 (2.6)	26 (13.5)	3 (1.6)	63 (33.9)	4 (2.2)
Vomiting	57 (29.7)	3 (1.6)	52 (27.1)	9 (4.7)	28 (15.1)	2 (1.1)
Fatigue	55 (28.7)	4 (2.1)	48 (25.0)	1 (0.5)	57 (30.7)	4 (2.2)
Arthralgia	49 (25.5)	1 (0.5)	84 (43.8)	18 (9.4)	83 (44.6)	11 (5.9)
Blood CPK	44 (22.9)	13 (6.8)	2 (1.0)	0	4 (2.2)	0
Headache	42 (21.9)	3 (1.6)	52 (27.1)	6 (3.1)	35 (18.8)	1 (0.5)
Constipation	42 (21.9)	0	27 (14.1)	0	12 (6.5)	1 (0.5)
Pyrexia	35 (18.2)	7 (3.7)	29 (15.1)	2 (1.0)	52 (28.0)	0
Asthenia	35 (18.2)	3 (1.6)	37 (19.3)	5 (2.6)	34 (18.3)	8 (4.3)
Abdominal pain	32 (16.7)	5 (2.6)	13 (6.8)	4 (2.1)	12 (6.5)	1 (0.5)
Vision blurred	30 (15.6)	0	4 (2.1)	0	4 (2.2)	0
GGT increased	29 (15.1)	18 (9.4)	21 (10.9)	9 (4.7)	21 (11.3)	6 (3.2)
Anemia	29 (15.1)	8 (4.2)	11 (5.7)	5 (2.6)	14 (7.5)	4 (2.2)
Rash	27 (14.1)	2 (1.0)	41 (21.4)	4 (2.1)	54 (29.0)	6 (3.2)
Hyperkeratosis	27 (14.1)	1 (0.5)	72 (37.5)	7 (3.7)	54 (29.0)	0
Dry skin	27 (14.1)	0	58 (30.2)	0	42 (22.6)	0
Myalgia	26 (13.5)	0	54 (28.1)	19 (9.9)	34 (18.3)	1 (0.5)
Alopecia	26 (13.5)	0	107 (55.7)	0	68 (36.6)	0
Dizziness	24 (12.5)	3 (1.6)	9 (4.7)	0	5 (2.7)	0
Abdominal pain upper	23 (12.0)	2 (1.0)	18 (9.4)	2 (1.0)	17 (9.1)	1 (0.5)
Hypertension	21 (10.9)	11 (5.7)	11 (5.7)	6 (3.1)	21 (11.3)	6 (3.2)
ALT increased	21 (10.9)	10 (5.2)	10 (5.2)	2 (1.0)	14 (7.5)	3 (1.6)
Pain in extremity	21 (10.9)	2 (1.0)	42 (21.9)	2 (1.0)	25 (13.4)	2 (1.1)
Pruritus	21 (10.9)	1 (0.5)	42 (21.9)	1 (0.5)	20 (10.8)	0
Edema peripheral	20 (10.4)	2 (1.0)	15 (7.8)	0	20 (10.8)	1 (0.5)

	COLUMBUS Part 1					
	Combo 450 N=192 n (%)		Enc 300 N=192 n (%)		Vem N=1862 n (%)	
Preferred Term	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Nasopharyngitis	20 (10.4)	0	11 (5.7)	0	18 (9.7)	0
AST increased	16 (8.3)	4 (2.1)	8 (4.2)	1 (0.5)	15 (8.1)	3 (1.6)
Hyperglycemia	9 (4.7)	4 (2.1)	6 (3.1)	4 (2.1)	0	0
Pleural effusion	4 (2.1)	4 (2.1)	3 (1.6)	2 (1.0)	2 (1.1)	1 (0.5)

Source: Reviewer generated table using COLUMBUS Part 1 SDTM.AE (cutoff 9 May 2016, submitted by Applicant)
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase.

Table 63: Incidence of TEAEs at the SOC level: COLUMBUS Part 1

	Combo 450 N=192 n (%)		Enc 300 N=192 n (%)		Vem N=1862 n (%)	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Gastrointestinal disorders	138 (71.9)	22 (11.5)	130 (67.7)	25 (13.0)	127 (68.3)	19 (10.2)
Skin and subcutaneous tissue disorders	125 (65.1)	6 (3.1)	184 (95.8)	43 (22.4)	170 (91.4)	38 (20.4)
General disorders and administration site conditions	122 (63.5)	24 (12.5)	123 (64.1)	21 (10.9)	130 (69.9)	24 (12.9)
Eye disorders	104 (54.2)	5 (2.6)	53 (27.6)	1 (0.5)	62 (33.3)	1 (0.5)
Investigations	103 (53.7)	47 (24.5)	71 (37.0)	17 (8.9)	77 (41.4)	14 (7.5)
Musculoskeletal and connective tissue disorders	102 (53.1)	5 (2.6)	149 (77.6)	43 (22.4)	125 (67.2)	19 (10.2)
Infections and infestations	97 (50.5)	19 (9.9)	82 (42.7)	6 (3.1)	92 (49.5)	9 (4.8)
Nervous system disorders	95 (49.5)	18 (9.4)	107 (55.7)	18 (9.4)	77 (41.4)	14 (7.5)
Respiratory, thoracic and mediastinal disorders	57 (29.7)	8 (4.2)	52 (27.1)	10 (5.2)	50 (26.9)	8 (4.3)
Metabolism and nutrition disorders	44 (22.9)	10 (5.2)	61 (31.8)	14 (7.3)	49 (26.3)	10 (5.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	44 (22.9)	5 (2.6)	72 (37.5)	11 (5.7)	82 (44.1)	22 (11.8)
Psychiatric disorders	42 (21.9)	3 (1.6)	64 (33.3)	6 (3.1)	31 (16.7)	0
Blood and lymphatic system disorders	40 (20.8)	11 (5.7)	20 (10.4)	9 (4.7)	30 (16.1)	9 (4.8)
Vascular disorders	36 (18.8)	12 (6.3)	36 (18.8)	7 (3.7)	36 (19.4)	6 (3.2)
Cardiac disorders	25 (13.0)	2 (1.0)	27 (14.1)	4 (2.1)	28 (15.1)	5 (2.7)
Injury, poisoning and procedural complications	25 (13.0)	2 (1.0)	16 (8.3)	3 (1.6)	28 (15.1)	4 (2.2)
Renal and urinary disorders	25 (13.0)	5 (2.6)	19 (9.9)	4 (2.1)	23 (12.4)	6 (3.2)
Reproductive system and breast disorders	19 (9.9)	0(0.0)	14 (7.3)	0	13 (7.0)	1 (0.5)
Ear and labyrinth disorders	12 (6.3)	0	11 (5.7)	1 (0.5)	8 (4.3)	0
Hepatobiliary disorders	7 (3.7)	4 (2.1)	3 (1.6)	1 (0.5)	9 (4.8)	2 (1.1)

Immune system disorders	6 (3.1)	0	12 (6.3)	2 (1.0)	8 (4.3)	1 (0.5)
Congenital, familial and genetic disorders	2 (1.0)	0	5 (2.6)	1 (0.5)	0	0
Endocrine disorders	2 (1.0)	0	4 (2.1)	0	3 (1.6)	0
Product issues	0		1 (0.5)	1 (0.5)	1 (0.5)	0
Social circumstances	0	0	1 (0.5)	0	0	0

Source: Reviewer generated table using COLUMBUS Part 1 SDTM.AE (cutoff 9 May 2016, submitted by Applicant)

Using FDA MAED Software, narrow scope MedDRA SMQs were analyzed to look for potential safety signals not identified through analysis of AEs by MedDRA system organ class, high level term, high level group term, or preferred term. The analysis did not identify any signals not previously identified.

Laboratory Findings

Table 64 summarizes the incidence of treatment emergent laboratory abnormalities occurring in ≥ 10% (all grades) or ≥ 2% (Grades 3-4) of patients in the Combo 450 arm of COLUMBUS Part 1. With the exception of CPK, overall, the laboratory abnormalities were similar among the arms given the expected differences due to chance and the longer exposure received in patients on the Combo 450 arm. In Part 1, patients in the Combo 450 arm experienced a significantly higher incidence of elevated CPK (58%) compared to the encorafenib monotherapy and vemurafenib arms (3% and 3.8% respectively). This is not unexpected with the addition of binimetinib as elevated CPK is a known class effect of MEK inhibitors.

Table 64: Incidence of Treatment-Emergent Laboratory Abnormalities (Changes from Baseline) Occurring in ≥ 10% (All Grades) or ≥ 2% (Grade3-4) of Patients with Combo 450: COLUMBUS Part 1

Laboratory Test	**Combo 450 N=192**		**Enc 300 N=192**		**Vem N=186**	
Hematology	**All Grades N (%)**	**Grade 3-4[1] N (%)**	**All Grades N (%)**	**Grade 3-4[2] n (%)**	**All Grades N (%)**	**Grade 3-4[3] N (%)**
Decreased hemoglobin	70 (36.5)	7 (3.6)	71 (37.0)	3 (1.6)	63 (33.9)	4 (2.2)
Decreased leukocytes	25 (13.0)	0	7 (3.6)	0	18 (9.7)	1 (0.5)
Decreased lymphocytes	25 (13.0)	4 (2.1)	29 (15.1)	2 (1.0)	56 (30.1)	12 (6.5)
Decreased neutrophils	25 (13.0)	6 (3.1)	9 (4.7)	2 (1.0)	9 (4.8)	1 (0.5)
Chemistry						
Increased ALT	56 (29.2)	11 (5.7)	29 (15.1)	3 (1.6)	50 (26.9)	4 (2.2)
Increased ALP	40 (20.8))	1 (0.5)	27 (14.1)	0	66 (35.5)	4 (2.2)
Increased AST	51 (26.6)	5 (2.6)	22 (11.5)	1 (0.5)	45 (24.2)	3 (1.6)
Increased CPK	111 (57.8)	10 (5.2)	6 (3.1)	0	7 (3.8)	0
Increased creatinine	178 (92.7)	7 (3.6)	147 (76.6)	1 (0.5)	171 (91.9)	2 (1.1)
Increased fasting glucose	53 (27.6)	10 (5.2)	52 (27.1)	8 (4.2)	37 (19.9)	5 (2.7)
Increased GGT	87 (45.3)	22 (11.5)	70 (36.5)	18 (9.4)	63 (33.9)	9 (4.8)

Laboratory Test	Combo 450 N=192		Enc 300 N=192		Vem N=186	
Increased magnesium	20 (10.4)	2 (1.0)	29 (15.1)	0	49 (26.3)	1 (0.5)
Decreased sodium	34 (17.7)	7 (3.6)	19 (9.9)	1 (0.5)	27 (14.5)	1 (0.5)

Source: Integrated Safety Summary Table 2-82 Submitted by Applicant June 30, 2017 (Reviewer confirmed underlying shift tables (ISS Table 3.1.4, 3.1.5) for Combo 450 arm using COLUMBUS Part 1 ADLB (cutoff 9 May 2016, submitted by Applicant).

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase;

Presented values represent new or worsening post-baseline abnormalities per National Cancer Institute CTCAE v4.03. Patients are counted only for the worst grade observed at post-baseline.

Baseline is defined as the last non-missing value prior to the first dose.

[1] Grade 4 laboratory test abnormalities limited to decreased neutrophils (n=2), increased creatine kinase (n=2) and increased fasting glucose (n = 1).

[2] Grade 4 laboratory test abnormalities limited to decreased neutrophils (n=1), increased fasting glucose (n=2) and increased GGT (n= 3).

[3] Grade 4 laboratory test abnormalities limited to decreased lymphocytes (n=1), decreased neutrophils (n=1), increased fasting glucose (n=1), and increased GGT (n=2).

Vital Signs

For COLUMBUS, vital signs were obtained during screening (within 21 days of initiating study treatment), Day 1 of each cycle, at end of treatment (EOT), and at the 30-day safety follow-up visit. Vital signs included blood pressure, temperature, pulse, and respiratory rate measurements.

Table 65 summarizes the incidence of newly occurring abnormal vitals signs for COLUMBUS Part 1. The vital signs where ≥ 5% of patients in the Combo 450 experienced newly occurring abnormal value are: low body temperature, weight gain, high systolic blood pressure, and high diastolic blood pressure. The incidence of newly occurring high systolic BP in the Combo 450 arm was higher than that observed in the encorafenib monotherapy arm (15% versus 8%) but similar to that observed in the vemurafenib arm. The reason for the difference between the Combo 450 and encorafenib monotherapy arms is not clear. It may be due to the higher dose of encorafenib or increased duration of exposure. Based on adverse event reports of related PTs (hypertension, essential hypertension, hypertensive crisis, blood pressure increased, blood pressure systolic increased, hypertensive cardiomyopathy, orthostatic hypertension), which may include new, preexisting, and worsening hypertension, no patient in the Combo 450 arm discontinued therapy due to hypertension while only 5 patients (2.6%) required dose interruption and/or dose modification. Overall, while 15% of patients in the Combo 450 arm experienced newly occurring high systolic blood pressure, similar in incidence to the control arm, it was rarely severe enough to interfere with therapy.

Table 65: Patients with Newly Occurring Notably Abnormal Vital Signs by: COLUMBUS Part 1

	COLUMBUS Part 1		
Vital Sign Category	**Combo 450 N=192 n/m (%) [1]**	**Enc 300 N=192 n/m (%)**	**Vem N=186 n/m (%)**
Sitting pulse rate (bpm) [2]			
High	1/186 (0.5)	7/184 (3.8)	8/182 (4.4)
Low	3/185 (1.6)	8/181 (4.4)	2/182 (1.1)
Sitting systolic BP (mmHg) [3]			
High	27/177 (15.3)	14/177 (7.9)	31/172 (17.9)
Low	7/188 (3.7)	3/184 (1.6)	1/182 (0.5)
Sitting diastolic BP (mmHg) [4]			
High	23/182 (12.6)	5/183 (2.7)	13/181 (7.2)
Low	9/188 (4.8)	6/185 (3.2)	5/184 (2.7)
Weight (kg) [5]			
High	44/187 (23.5)	9/184 (4.9)	8/184 (4.3)
Low	2/187 (1.1)	8/184 (4.3)	13/184 (7.1)
Body temperature (°C) [6]			
High	19/185 (10.3)	11/176 (6.3)	17/181 (9.4)
Low	76/132 (57.6)	73/134 (54.5)	57/141 (40.4)

Source: Summary of Clinical Safety Table 4-1 submitted to Module 2.7.4, June 30, 2016. Reviewer confirmed for Combo 450 arm using COLUMBUS Part 1 ADVS (cutoff 9 May 2016, submitted Applicant)
Abbreviations: BP = blood pressure; bpm = beats per minute; °C = degree(s) Celsius; kg = kilogram(s); mg = milligram(s); mmHg = millimeter(s) of mercury;
[1] m = number of patients at risk for a specific category with a non-missing value at baseline and post-baseline, n = number of patients who met the criteria at least once.
[2] Low/high pulse rate [bpm]: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm/≥ 120 bpm with increase from baseline of ≥ 15 bpm Low/high.
[3] Low/high systolic BP [mmHg]: ≤ 90 mmHg with decrease from baseline of ≥ 20 mmHg/≥ 160 mmHg with increase from baseline of ≥ 20 mmHg.
[4] Low/high diastolic BP [mmHg]: ≤ 50 mmHg with decrease from baseline of ≥ 15 mmHg/≥ 100 mmHg with increase from baseline of ≥ 15 mmHg.
[5] Weight [kg]: ≥ 20% decrease from baseline/≥ 10% increase from baseline.
[6] Low/high body temperature [°C]: ≤ 36°C/≥ 37.5°C.

Electrocardiograms (ECGs)

For patients enrolled on COLUMBUS, standard 12-lead Electrocardiograms (ECGs) were to be performed during screening, Day 1 Cycles 1, 2, and 3, every 3 cycles thereafter (every 12 weeks), EOT, and at the 30-day safety follow-up. Baseline measurements were based on the average of three screening ECGs preformed in 5 minute intervals.

Table 66 summarizes the proportion of patients who demonstrated changes in QTcF for each arm in COLUMBUS Part 1 as well as the Combo 450, binimetinib 45 mg BID, and Encorafenib 300 mg monotherapy pools. A smaller proportion of patients demonstrated an increased > 30 ms from baseline in the Combo 450 arm (27%) compared to the vemurafenib arm (43%) while a similar proportion demonstrated an increased over 60 msec. A lower proportion of patients had a new QTcF > 450 ms in the Combo 450 arm (14%) compared to the encorafenib monotherapy

arm (21%) and the vemurafenib arm (24%). The proportion of patients with new QTcF over 480 ms is low and similar among all arms.

No other notable ECG changes were identified. No patients on any arm experienced an increase in QRS more than 25% to a value above 110 ms.

Table 66: Patients with Notable ECG Value Changes: COLUMBUS Part 1

	COLUMBUS Part 1			Pooled Data Sets	
	Combo 450 N=192 n/m (%) [1]	**Enc 300 N=192 n/m (%)**	**Vem N=186 n/m (%)**	**Bini 45 mg BID N=427 n/m (%)**	**Enc 300 N=217 n/m (%)**
QTcF (ms) [2]					
Increase from baseline > 30 ms	50/186 (26.9)	52/179 (29.1)	76 (179 (42.5)	82/412 (19.9)	65/204 (31.9)
Increase from baseline > 60 ms	10/186 (5.4)	7/179 (3.9)	10/179 (5.6)	11/412 (2.7)	7/204 (3.4)
New > 450 ms	25/178 (14.0)	36/171 (21.1)	42/174 (24.1)	11/412 (2.7)	7/204 (3.4
New > 480 ms	7/186 (3.8)	7/177 (4.0)	5/179 (2.8)	51/384 (13.3)	44/194 (22.7)
New > 500 ms	1/186 (0.5)	5/178 (2.8)	3/179 (1.7)	15/411 (1.2)	5/203 (2.5)
QRS: Increase from baseline > 25% to a value > 110 ms	0	0	0	6/150 (4.0)	0

Source: Summary of Clinical Safety Table 4-2 submitted to Module 2.7.4, June 30, 2016, results from pooled Combo 450 arm confirmed by QT-IRT reviewer.

[1] m = number of patients at risk for a specific category with a non-missing value at baseline and post-baseline n = number of patients who met the criteria at least once.

[2] QTcF = QT interval corrected for heart rate using Frederica's formula.

QT

DOP2 requested consultations for evaluation of the encorafenib and binimetinib applications from the Interdisciplinary Review Team for QT Studies (QT-IRT). This section summarizes the findings from those consultations.

The Applicant did not conduct a dedicated QT study to evaluate QT prolongation for either binimetinib or encorafenib.

For the encorafenib and binimetinib applications, the Applicant submitted three cardiac studies:

- Study CP-16-002 is a cardiac safety analysis performed by the Applicant to evaluate the potential of binimetinib and its metabolite AA00426032 to delay cardiac repolarization as measured by QTc prolongation. The analysis is based on pooled ECG and PK data pooled from 7 clinical trials in healthy subjects and cancer patients (ARRY-162-0601, ARRY-162-0602, CMEK162A2101J, ARRAY-162-111, CMEKX2201, CMEK162X1101, and CMEK162A2301).

- Study CP-17-005 is a cardiac safety analysis performed by the Applicant to evaluate the potential of therapeutic concentrations of encorafenib to delay cardiac repolarization as measured by QT prolongation. The analysis was completed using encorafenib concentrations and ECG measurements from clinical trial CLGX818X2101, a dose escalation and expansion study in patients with metastatic melanoma and metastatic colorectal carcinoma conducted with expanded ECG monitoring.
- Study CP-17-006 is a cardiac safety analysis performed by the Applicant to evaluate the potential therapeutic concentrations of the combination of encorafenib and binimetinib that could delay cardiac repolarization as measured by QT prolongation. The analysis was completed using encorafenib concentrations and ECG measurements from clinical trials CMEK162X2110, CLGX818X2109, and CMEK162B2301.

The QT-IRT performed a review and analysis of the binimetinib data and study submitted with the application. The analysis utilized the same 7 clinical trials involving binimetinib monotherapy. The QT-IRT review concluded the following:

- In the pooled analysis across 7 clinical trials in subjects and patients receiving binimetinib, a relatively flat relationship between delta QTcF and concentrations of binimetinib or its metabolite AA00426032 was observed. Based on the observed concentration – delta QTcF relationship, no large QTc prolongation (20ms) is estimated following a dose of 45 mg BID.

No dose modifications for binimetinib for QT prolongation are recommended by QT-IRT. QT-IRT recommends modification of Section 12.2 of the label under Cardiac Electrophysiology to include a summary of the QTc prolongation assessment. This is described in Section 11 of this review.

The QT-IRT performed a review and analysis of the encorafenib monotherapy and encorafenib with binimetinib combination data and studies submitted with the application. The review concludes the following:

- Encorafenib is associated with dose-dependent QTc interval prolongation. The conclusion is based on data from studies CLGX818X2109 and CLGX818X20101 which showed an upper bound of the 2-sided 90% confidence interval > 20% for mean change in QTcF from baseline for encorafenib 450 mg once daily monotherapy and encorafenib 450 one daily in combination with binimetinib 45 mg twice daily.
- Although encorafenib shows a dose- and concentration- dependent QTc interval prolongation, there is a lack of direct relationship between concentrations of encorafenib and QTc effects because of temporal increase in QTc effects. Therefore, a linear C-QTc model that assumes a direct relationship between plasma concentration and QTc cannot be used for analysis.

QT-IRT agreed with Array's proposed dose modifications for encorafenib to be included in the label which are summarized below:

- [redacted] QTcF > 500 ms and [redacted] ≤ [redacted] ms [redacted], withhold BRAFTOVI until QTcF [redacted] 500 ms. [redacted] discontinued if more than one recurrence
- [redacted] QTcF > 500 ms and [redacted] > 60 ms [redacted], permanently discontinue BRAFTOVI.

QT-IRT recommended the addition of QT Prolongation as a new Warnings and Precautions with additional information provided in Section 12.2 under Cardiac Electrophysiology. Section 11 of this review presents the final agreed upon labeling language regarding QTc prolongation.

Echocardiograms and MUGA scans

COLUMBUS required patients have adequate cardiac function as measured by MUGA scan or echocardiogram with an LVEF ≥ 50%. Cardiac imaging was to be performed at screening, Day 1 of Cycles 2 and 3, and every 12 weeks (3 cycles) thereafter, at end of treatment, at 30-day safety follow up visit, and as clinically indicated during the treatment period. LVEF was summarized by treatment arm as change from baseline over time, worst change, and abnormalities.

Table 67 summarizes the incidence of worst post-baseline LVEF value based on CTCAE Grade for COLUMBUS Part 1. When compared to the encorafenib monotherapy or the vemurafenib arm, the Combo 450 regimen resulted in a higher proportion of patients experiencing a worsening of LVEF as measured by ECHO/MUGA. This increase is due to an increased in Grade 2 toxicity. In the Combo 450 arm, almost 31% of patients experienced a worsening of cardiac function (29.2% Grade 2, 1.6% Grade 3), while in the encorafenib monotherapy arm (Part 1), only 11% of patients experienced a worsening of cardiac function (9.4% Grade 2, 1.6% Grade 3).

Table 67: Incidence Worst Post-baseline LVEF Grade: COLUMBUS Part 1

	COLUMBUS Part 1		
Worst Post-baseline CTCAE Grade [1]	**Combo 450 N= 192 n (%)**	**Enc 300 N= 192 n (%)**	**Vem N=186 n (%)**
Grade 0	127 (66.1%)	161 (83.9)	161 (86.6)
Grade 2	56 (29.2)	18 (9.4)	16 (8.6)
Grade 3	3 (1.6)	3 (1.6)	2 (1.1)
Grade 4	0	0	0
Missing [2]	6 (3.1)	10 (5.2)	7 (3.8)

Source: CSR COLUMBUS Part 1 Table 88 submitted to application June 30, 2017

[1] Grade 0: Non-missing value below Grade 2
Grade 2: LVEF between 40% and 50% or absolute reduction from baseline ≥ 10% and ≤ 20%
Grade 3: LVEF between 20% and 39% or absolute reduction from baseline ≥ 20%
Grade 4: LVEF below 20%

[2]Missing data were due to patients who died or withdrew consent prior to the first dose of study treatment. Patients were counted only for the worse grade observed post-baseline. Baseline % is based on N. Percentage for worst post-baseline value is based on Baseline n.

8.2.4. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest

Based on preclinical data for binimetinib and encorafenib, data from earlier clinical trials, and known class effects for MEK and BRAF inhibitors, the applicant identified a set of adverse events of special interests (AESIs). The applicant derived the AESI groupings using standardized MedDRA queries or by modifying high level terms modified to remove PTs not felt to reflect the underlying pathology for the specific AESI group. Some AESIs were defined through use of a customized list or may comprise a single PT. The application considered the following AESIs:

- Ocular AESI groupings: retinopathy excluding RVO, RVO, uveitis-type events
- Liver-related AESI groupings: liver function test abnormalities, hepatic failure
- Myopathy/rhabdomyolysis-related AESI groupings: muscle enzyme/protein changes, myopathy, rhabdomyolysis
- Dermatologic-related AESI groupings: rash, photosensitivity, nail disorders, skin infections, severe cutaneous adverse reactions, PPE syndrome
- Cardiac related AESI groupings: bradycardia, tachycardia, left ventricular dysfunction
- Cutaneous malignancies AESI groupings: cutaneous squamous cell carcinoma (cuSCC), cutaneous non-squamous cell carcinoma, melanomas
- Additional AESI groupings: hypertension, peripheral edema, hemorrhage, pneumonitis, venous thromboembolism, tachycardia, acute renal failure, facial paresis

Table 68 shows the incidence of each AESI for all arms in COLUMBUS Part 1 for all grades and Grades 3-4 in order of decreasing frequency for Combo 450 arm.

The following AESIs occurred with greater frequency (≥5% increase) in the Combo 450 arm when compared to the vemurafenib arm but with similar frequency between the encorafenib monotherapy and vemurafenib arm: retinopathy excluding RVO (+36%), muscle enzyme/ protein changes (+21%), hemorrhage (+10%), and left ventricular dysfunction (+7%). For these AESIs, the increased toxicity observed in patients receiving Combo 450 compared to those receiving vemurafenib appears due to the addition of the MEK inhibitor binimetinib. These events have been previously associated with other MEK inhibitors.

The following AESIs, while not occurring with greater frequency (≤ 5% difference), shows an increase in Grade 3-4 events (≥2% increase) in the Combo 450 arm compared to the vemurafenib arm: liver function test abnormalities (+11%), hypertension (+3%), and skin infections (+2%). A similar increase in severity is not observed in patients in the encorafenib monotherapy arm compared to patients in the vemurafenib arm, suggesting that the increased incidence in Grade 3-4 events observed in patients receiving Combo 450 compared to those receiving vemurafenib is due to the addition of the MEK inhibitor binimetinib. Hepatotoxicity is a known toxicity associated with other MEK inhibitors.

The following AESIs occurred with decreased frequency in the Combo 450 and in the encorafenib monotherapy arms (≤ -5%) when compared to the vemurafenib arm: rash (-33% Combo 450, -10% encorafenib), photosensitivity (-33%, -33%), cutaneous squamous cell carcinoma (-14%, -9%). The decrease in the incidence in photosensitivity appears to be due to less BRAF inhibitor related toxicity, while the decrease in cutaneous squamous cell carcinoma and rash appears due to both less toxicity from the BRAF inhibitor encorafenib as well as from the addition of the MEK inhibitor binimetinib.

The following AESIs occur at a greater frequency (≥5% increase) in the encorafenib monotherapy arm when compared to the vemurafenib arm: palmar-plantar erythrodysaesthsia syndrome (+37%), myopathy (11%), and facial paresis (7%). For these AESIs, the increase in incidence with encorafenib is negated by the addition of binimetinib. These events have been associated with other BRAF inhibitors.

Table 68: Incidence of AESI All Grades and Grades 3-4: Columbus Part 1

	COLUMBUS Part 1		
AESI	**Combo 450 N=192 % All Grades (% Gr 3-4)**	**Enc 300 N=192 % All Grades (% Gr 3-4)**	**Vem N=186 % All Grades (% Gr 3-4)**
Retinopathy excluding RVO	48.4 (2.6)	13.5 (0)	12.4 (0)
Rash	26.0 (1.0)	49.5 (5.2)	59.7 (13.4)
Liver Function Test Abnormalities	25.0 (14.6)	14.6 (5.7)	21 (3.8)
Muscle enzyme/ protein changes	22.9 (6.8)	1.6 (0)	2.2 (0)
Hemorrhage	18.2 (3.1)	12.5 (2.1)	8.1 (1.6)
Myopathy	16.7 (0)	31.3 (9.9)	19.9 (0.5)
Peripheral edema	12.5 (1.0)	9.9 (0)	11.8 (1.1)
Hypertension	11.5 (5.7)	6.3 (3.1)	11.3 (3.2)
Skin infections	11.5 (2.1)	12.0 (0.5)	14 (0)
Left ventricular dysfunction	7.8 (1.6)	2.1 (1.0)	1.1 (0)
PPES	6.8 (0)	51.0 (13.5)	14 (1.1)
Venous Thromboembolism	5.2 (1.0)	3.1 (1.0)	1.6 (0.5)
Photosensitivity	4.7 (0.5)	4.7 (0)	37.6 (1.6)
Acute renal failure	3.6 (2.6)	2.6 (1.6)	4.8 (1.6)
Uveitis type events	3.6 (0.5)	0.5 (0)	3.8 (0)
Cutaneous squamous cell carcinoma	2.6 (0)	7.8 (0)	16.7 (6.5)
Cutaneous non-squamous cell carcinoma	2.1 (0)	1.0 (0.5)	2.7 (0.5)
Nail disorders	1.6 (0)	3.1 (0)	0 (0)
Tachycardia	1.6 (0.5)	6.3 (1.0)	5.4 (0.5)
Bradycardia	1.0 (0)	0.5 (0)	1.1 (0.5)
Facial paresis	1.0 (0.5)	7.3 (1.6)	0.5 (0)
Hepatic failure	0.5 (0.5)	0 (0)	0 (0)
Pneumonitis	0.5 (0)	(1.0) (0)	0.5 (0.5)

Rhabdomyolysis	0.5 (0.5)	0 (0)	0 (0)
Severe Cutaneous Adverse Reactions	0.5 (0)	1.0 (0.5)	4.3 (2.7)
Melanomas	0 (0)	5.2 (1.6)	4.3 (3.2)
Retinal Vein Occlusion	0 (0)	0.5 (0.5)	0 (0)

Source: Reviewer generated table using ISS_ADAESI (cutoff 9 May 2016, submitted by Applicant)
Abbreviations: PPES = Palmar-plantar Erythrodysaesthesia Syndrome

Adverse Drug Reactions

Based on all available safety data, the applicant identified a set of adverse drug reactions (ADRs). A complete list of the ADRs and associated PTs is shown in Table 69. Table 70 shows the incidence for each ADR for each arm of COLUMBUS Part 1.

Table 69: Adverse Drug Reactions Groupings

ADR Grouping	Preferred Terms
Abdominal pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort, Gastrointestinal pain, Hepatic pain, Pelvic pain
Acneiform dermatitis	Acne, Acne pustular, Dermatitis acneiform
Alopecia	Alopecia, Alopecia totalis, Diffuse alopecia
Arthralgia	Arthralgia, Arthropathy, Joint Stiffness
Back pain	Back pain
Basal cell carcinoma	Basal cell carcinoma
Colitis	Colitis, Colitis ulcerative, Enterocolitis, Proctitis
Constipation	Constipation
Cutaneous squamous cell carcinoma	Keratoacanthoma, Lip squamous cell carcinoma, Squamous cell carcinoma, Squamous cell carcinoma of skin
Diarrhea	Diarrhea, Frequent bowel movements
Dizziness	Balance disorder, Dizziness, Vertigo
Drug hypersensitivity	Angioedema, Cutaneous vasculitis, Drug eruption, Drug hypersensitivity, Hypersensitivity, Hypersensitivity vasculitis, Urticaria, Vasculitis
Dry skin	Asteatosis, Dry skin, Xeroderma, Xerosis
Dysgeusia	Ageusia, Dysgeusia, Hypogeusia
Erythema	Erythema, Generalized erythema, Plantar erythema
Facial paresis	Facial nerve disorder, Facial paralysis, Facial paresis
Fatigue	Asthenia, Fatigue, Lethargy
Hemorrhage	Anal hemorrhage, Cerebral hemorrhage, Conjunctival hemorrhage, Diarrhea hemorrhagic, Epistaxis, Gastric hemorrhage, Gastric ulcer hemorrhage, Gastrointestinal hemorrhage, Hematemesis, Hematochezia, Hematospermia, Hematuria, Hemoptysis, Hemorrhage, Hemorrhagic cyst, Hemorrhoid hemorrhage, Intracranial tumor hemorrhage, Large intestinal hemorrhage, Lower gastrointestinal hemorrhage, Melena, Menorrhagia, Metrorrhagia, Mucosal hemorrhage, Occult blood, Polymenorrhea, Postmenopausal hemorrhage, Post procedural hemorrhage, Pulmonary alveolar hemorrhage, Rectal hemorrhage, Retinal hemorrhage, Subdural hematoma, Tumor hemorrhage, Upper gastrointestinal hemorrhage, Uterine hemorrhage, Vaginal hemorrhage, Wound hemorrhage
Headache	Headache, Head discomfort, Migraine
Hyperkeratosis	Hyperkeratosis, Hyperkeratosis follicularis et parafollicularis, Keratosis pilaris, Lichenoid keratosis, Palmoplantar keratoderma, Parakeratosis, Skin hyperplasia
Hypertension	Blood pressure increased, Essential hypertension, Hypertension, Hypertensive

	cardiomyopathy, Hypertensive crisis, Orthostatic hypertension
Left ventricular dysfunction (Cardiomyopathy)	Cardiac failure, Ejection fraction abnormal, Ejection fraction decreased, Left ventricular dysfunction
Myopathy	Muscle injury, Muscle spasms, Muscular weakness, Myalgia, Myopathy, Myositis
Nausea	Nausea
Neuropathy	Dysesthesia, Hyperesthesia, Hypoesthesia, Neuralgia, Neuropathy peripheral, Paranesthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Polyneuropathy, Sciatica, Sensory disturbance, Sensory loss
Pain in extremity	Pain in extremity
Palmar-plantar erythrodysesthesia syndrome	Palmar-plantar erythrodysesthesia syndrome
Pancreatitis	Pancreatitis, Pancreatitis acute
Panniculitis	Erythema nodosum, Panniculitis
Peripheral edema	Fluid retention, Generalized edema, Local swelling, Localized edema, Edema, Edema genital, Edema peripheral, Penile edema, Peripheral swelling, Scrotal edema
Pruritus	Pruritus, Pruritus generalized, Pruritus genital
Pyrexia	Body temperature increased, Hyperpyrexia, Hyperthermia, Pyrexia
Rash	Exfoliative rash, Rash, Rash erythematous, Rash follicular, Rash generalized, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash papular, Rash pruritic, Rash vesicular
Serious retinopathy/Retinal pigment epithelial detachment (RPED)	Chorioretinitis, Chorioretinopathy, Cystoid macular edema, Detachment of macular retinal pigment epithelium, Detachment of retinal pigment epithelium, Exudative retinopathy, Macular detachment, Macular edema, Maculopathy, Metamorphopsia, Retinal detachment, Retinal disorder, Retinal exudates, Retinal edema, Retinal pigment epitheliopathy, Retinitis, Retinopathy, Subretinal fluid
Rhabdomyolysis	Rhabdomyolysis
Skin papilloma	Blepharal papilloma, Oral papilloma, Papilloma, Skin papilloma
Uveitis	Iritis, Iridocyclitis, Uveitis
Venous thromboembolism	Deep vein thrombosis, Embolism, Embolism venous, Mesenteric vein thrombosis, Pelvic venous thrombosis, Peripheral artery thrombosis, Phlebitis, Phlebitis superficial, Portal vein thrombosis, Pulmonary embolism, Thrombophlebitis, Thrombophlebitis superficial, Thrombosis, Venous thrombosis
Visual impairment	Vision blurred, Visual acuity reduced, Visual impairment
Vomiting	Retching, Vomiting

Source: ISS Study Report Table 2-78 (Submitted by Applicant)

Table 70: Incidence of ADR by General Organ System: COLUMBUS Part 1

ADR	Combo 450 (N=192) All Grades % (Gr 3-4 %)	Enc 300 (N=192) All Grades % (Gr 3-4 %)	Vem (N=186) All Grades % (Gr 3-4 %)
General Disorders and adminsitration site conditions			
Fatigue	43.2 (3.1)	41.7 (3.1)	46.2 (6.5)
Pyrexia	18.2 (4.2)	15.6 (1.0)	29.6 (0.0)
Peripheral edema	13.0 (1.0)	9.4 (0.0)	14.5 (1.1)
Drug hypersensitivity	3.6 (0.0)	4.7 (0.5)	4.8 (1.6)
Gastrointestinal disorders			

ADR	Combo 450 (N=192) All Grades % (Gr 3-4 %)	Enc 300 (N=192) All Grades % (Gr 3-4 %)	Vem (N=186) All Grades % (Gr 3-4 %)
Nausea	41.1 (1.6)	38.5 (4.2)	33.9 (1.6)
Diarrhea	36.5 (2.6)	13.5 (1.6)	33.9 (2.2)
Vomiting	29.7 (1.6)	27.1 (4.7)	15.6 (1.1)
Abdominal pain	28.1 (3.6)	16.7 (3.1)	15.6 (1.1)
Constipation	21.9 (0.0)	14.1 (0.0)	6.5 (0.5)
Colitis	2.1 (1.0)	1.0 (0.0)	0.5 (0.0)
Pancreatitis	1.0 (1.0)	0.0 (0.0)	1.1 (0.5)
Musculoskeletal and connective tissue disorders			
Arthralgia	25.5 (0.5)	44.3 (9.4)	45.7 (5.9)
Myopathy	23.4 (0.0)	33.3 (9.9)	22.0 (0.5)
Pain in extremity	10.9 (1.0)	21.9 (1.0)	13.4 (1.1)
Back pain	9.4 (0.5)	15.1 (2.6)	5.9 (1.6)
Rhabdomyolysis	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)
Skin and subcutaneous tissue disorders			
Hyperkeratosis	22.9 (0.5)	57.3 (4.7)	49.5 (1.1)
Rash	22.4 (1.0)	41.1 (4.2)	53.2 (13.4)
Dry skin	16.1 (0.0)	37.5 (0.0)	26.3 (0.0)
Pruritus	12.5 (0.5)	30.7 (0.5)	21.0 (1.1)
Alopecia	14.1 (0.0)	56.3 (0.0)	37.6 (0.0)
PPES	6.8 (0.0)	51.0 (13.5)	14.0 (1.1)
Erythema	7.3 (0.0)	15.6 (1.6)	17.2 (0.5)
Acneiform dermatitis	3.1 (0.0)	8.3 (0.0)	6.5 (0.0)
Panniculitis	1.6 (0.0)	0.5 (0.0)	3.2 (0.5)
Nervous System Disorder			
Headache	21.9 (1.6)	28.1 (3.6)	19.9 (0.5)
Dizziness	15.1 (2.6)	6.3 (0.5)	4.3 (0.0)
Neuropathy	12.0 (1.0)	21.9 (1.0)	13.4 (1.6)
Dysgeusia	5.7 (0.0)	13.0 (0.0)	10.2 (0.0)
Facial paresis	1.0 (0.5)	7.3 (1.6)	0.5 (0.0)
Eye disorders			
Visual impairment	20.3 (0.0)	5.7 (0.0)	4.3 (0.0)
RPED	19.8 (2.6)	2.1 (0.0)	1.6 (0.0)
Uveitis	3.6 (0.5)	0.5 (0.0)	3.8 (0.0)
Cardiac and Vascular disorders			
Hemorrhage	18.8 (3.1)	10.9 (2.1)	8.6 (1.6)
Hypertension	11.5 (5.7)	5.7 (3.1)	11.3 (3.2)
Left ventricular dysfunction (Cardiomyopathy)	7.8 (1.6)	2.1 1.0)	0.5 (0.0)
Venous thromboembolism	5.7 (1.6)	3.1 (1.0)	2.2 (0.5)
Neoplasms benign, malignant, and unspecified			
Skin papilloma	7.3 (0.0)	10.4 (0.0)	19.4 (0.0)

ADR	Combo 450 (N=192) All Grades % (Gr 3-4 %)	Enc 300 (N=192) All Grades % (Gr 3-4 %)	Vem (N=186) All Grades % (Gr 3-4 %)
Cutaneous squamous cell carcinoma	2.6 (0.0)	7.8 (0.0)	17.2 (7.0)
Basal cell carcinoma	1.6 (0.0)	1.0 (0.5)	1.6 (0.5)
Source: Reviewer generated table using ISS_ADDR (cutoff 9 May 2016, submitted by Applicant) **Abbreviations:** PPES = palmar-plantar erythrodysesthesia; RPED = retinal pigment epithelial detachment.			

Combo 450 versus Vemurafenib Monotherapy

The following ADRs were observed more frequently (≥5% difference) in patients in the Combo 450 arm when compared to patients in the vemurafenib arm: RPED (+18.2), visual impairment (+16.0), constipation (+15.4), vomiting (+ 14.1), abdominal pain (+12.5), dizziness (+10.8), hemorrhage (+10.1), left ventricular dysfunction (+7.3), nausea (+7.3). With the exception of constipation and vomiting, a similar increase in frequency is not observed when comparing encorafenib to vemurafenib arms; therefore, the increased toxicity for these ADRs is due to the addition of binimetinib. These ADRs are consistent with toxicities known to be associated with MEK inhibitors.

The following ADRs were observed less frequently (≥5% difference) in patients in the Combo 450 arm when compared to patients in the vemurafenib arm: rash (-30.8), hyperkeratosis (-26.5), alopecia (-23.6), arthralgia (-20.2), cutaneous squamous cell carcinoma (-14.6), skin papilloma (-12.1), pyrexia (-11.3), dry skin (-10.2), erythema (-9.9), pruritus (-8.5), PPES (-7.2). Of these ADRs, a similar decrease is not observed when comparing encorafenib to vemurafenib arms for the following: hyperkeratosis, alopecia, arthralgia, dry skin, erythema, pruritus, and PPES. For these ADRS, the decrease in observed toxicity is due to the addition of binimetinib. For the following ADRs, a decrease is also observed when comparing encorafenib and vemurafenib arms: rash, cutaneous squamous cell carcinoma, skin papilloma, pyrexia. For these ADRs, the decrease in toxicity observed in the Combo 450 arm is due both to the comparative safety profile of encorafenib as well as to the addition of a MEK inhibitor to a BRAF inhibitor.

Encorafenib 300 monotherapy versus Vemurafenib Monotherapy

The following ADRs were observed more frequently (≥ 5% difference) in patients in the encorafenib monotherapy arm when compared to patients in the vemurafenib arm: PPES (+37.1), alopecia (+18.6), vomiting (+11.5), myopathy (+11.3), dry skin (+11.2), pruritus (+9.8), back pain (+9.2), neuropathy (+8.4), pain in extremity (+8.4), headache (+8.2), hyperkeratosis (+7.8), constipation (+ 7.6), facial paresis (+ 6.8). With the exception of vomiting and constipation, all of these ADRs were attenuated by the addition of binimetinib.

The following ADRs were observed less frequency (≥5% difference) in patients in the encorafenib monotherapy arm when compared to patients in the vemurafenib arm: diarrhea (-20.3), pyrexia (-13.9), rash (-12.1), cutaneous squamous cell carcinoma (-8.9), hypertension (-5.6), peripheral edema (-5.1).

Common ADRs associated with the Combo 450 regimen and Assessment of Contribution to Toxicity

The most common ADRs (≥20% all grades) for the combination 450 arm are: fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), arthralgia (26%), myopathy (23%), hyperkeratosis (23%), rash (22%), headache (22%), constipation (22%), visual impairment (20%), and RPED (20%). Additionally, hypertension had a frequency of Grade 3-4 events ≥5%: hypertension (6%).

For the following common ADRs (≥ 10%), there was less than a 5% difference (increase or decrease) in frequency between the combo 450 arm and the encorafenib monotherapy arm: peripheral edema (+3.6), vomiting (+2.6), pyrexia (+2.6), nausea (+2.6), fatigue (+1.6). For these ADRs, the increase in toxicity with addition of binimetinib and/or the higher dose of encorafenib is minimal.

For the following common ADRs, there was a ≥ 5% increase in frequency from the encorafenib monotherapy arm to the Combo 450 arm indicating the addition of the binimetinib and/or the increase in encorafenib dose added to the overall toxicity in the Combo 450 arm*:* diarrhea (+22.9), RPED (+17.7), visual impairment (+14.6), abdominal pain (+11.5), dizziness (+8.9), hemorrhage (+7.8), constipation (+7.8), hypertension (+5.7). The low incidence of RPED (2.1%) in the encorafenib monotherapy arm indicates that the toxicity for this RPED observed in the combination 450 arm is due almost exclusively to the binimetinib.

For the remaining ADRs, the increase in frequency observed in the Combo 450 arm could be due to the higher dose of encorafenib and/or the addition of binimetinib. The results of an exploratory comparison of the incidence of ADRs between Combo 300 and Combo 450 is discussed below. It is noted here that of these ADRs, only diarrhea occurs more frequently (≥5%) in the Combo 450 arm than in the Combo 300 arm. This suggests that, with the exception of diarrhea, the increase in frequency of ADRs observed in the Combo 450 is due primarily to the addition of binimetinib.

For the following common ADRs, there was a ≥ 5% decrease in frequency from the encorafenib monotherapy arm to the Combo 450 arm: alopecia (-42.2%), hyperkeratosis (-34.4%), dry skin (-21.4), arthralgia (-18.8), rash (-18.7%), pruritus (-18.2%), pain in extremity (-10.9%), neuropathy (-9.9%), myopathy (-9.9%), headache (-6.3%), For these ADRs, the addition of binimetinib to encorafenib attenuated the toxicity associated with encorafenib. This phenomenon has been observed in other BRAF/MEK combination regimens although the set of ADRs in which this occurs appears broader with encorafenib and binimetinib. This is discussed in more detail below.

Treatment Modifications for ADRs

The COLUMBUS protocol specified detailed dose modifications (discontinuations, reductions, and/or interruptions) for anticipated toxicities. Depending on the toxicity, modifications were made to encorafenib and binimetinib, to encorafenib only, or to binimetinib only. Table 71 shows the frequency of treatment modifications for Combo 450 and encorafenib monotherapy arms in COLUMBUS Part 1. The frequency of discontinuations for any ADR is similar between

arms while the frequency of reductions and interruptions is higher in the encorafenib monotherapy arm compared to the Combo 450 arm.

Table 71: Frequency of Treatment Discontinuations, Reductions, and Interruptions by Adverse Drug Reaction: COLUMBUS Part 1 COMBO 450 and Encorafenib Monotherapy

	COLUMBUS Part 1					
	Combo 450 N=192			Enc 300 N=192		
Adverse Drug Reaction	**Discontinuations n (%)**	**Reductions n (%)**	**Interruptions n (%)**	**Discontinuations n (%)**	**Reductions n (%)**	**Interruptions n (%)**
ANY ADR	15 (7.8)	20 (10.4)	74 (38.5)	17 (8.9)	47 (24.5)	104 (54.2)
Abdominal pain	1 (0.5)	1 (0.5)	6 (3.1)	0	1 (0.5)	6 (3.1)
Acneiform dermatitis	0	0	2 (1.0)	0	0	2 (1.0)
Alopecia	0	0	1 (0.5)	0	1 (0.5)	2 (1.0)
Amylase increased	1 (0.5)	1 (0.5)	2 (1.0)	0	0	0
Anemia	0	0	4 (2.1)	0	0	2 (1.0)
Arthralgia	0	1 (0.5)	3 (1.6)	1 (0.5)	8 (4.2)	16 (8.3)
Back pain	0	0	0	0	3 (1.6)	2 (1.0)
Basal cell carcinoma	0	0	1 (0.5)	0	0	0
ALP Increased	1 (0.5)	0	4 (2.1)	0	1 (0.5)	0
CPK Increase	1 (0.5)	0	6 (3.1)	0	0	0
Colitis	0	1 (0.5)	2 (1.0)	0	0	1 (0.5)
Constipation	0	0	1 (0.5)	0	1 (0.5)	0
Diarrhea	1 (0.5)	1 (0.5)	6 (3.1)	2 (1.0)	0	4 (2.1)
Dizziness	0	1 (0.5)	4 (2.1)	0	0	0
Drug hypersensitivity	0	0	0	2 (1.0)	2 (1.0)	3 (1.6)
Dry skin	0	1 (0.5)	0	0	1 (0.5)	1 (0.5)
Erythema	0	0	1 (0.5)	0	0	5 (2.6)
Facial paresis	0	0	1 (0.5)	2 (1.0)	1 (0.5)	6 (3.1)
Fatigue	1 (0.5)	2 (1.0)	4 (2.1)	0	4 (2.1)	9 (4.7)
Hemorrhage	3 (1.6)	0	2 (1.0)	0	0	2 (1.0)
Headache	2 (1.0)	1 (0.5)	1 (0.5)	2 (1.0)	2 (1.0)	11 (5.7)
Hyperkeratosis	0	2 (1.0)	4 (2.1)	2 (1.0)	8 (4.2)	9 (4.7)
Hypertension	0	1 (0.5)	4 (2.1)	0	0	1 (0.5)
LV dysfunction	0	0	12 (6.3)	2 (1.0)	0	0
Lipase increased	0	1 (0.5)	3 (1.6)	0	0	1 (0.5)
Myopathy	0	0	4 (2.1)	1 (0.5)	8 (4.2)	22 1 (1.5)
Nausea	0	2 (1.0)	14 (7.3)	0	6 (3.1)	11 (5.7)
Neuropathy	0	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	2 (1.0)
Pain in extremity	0	0	1 (0.5)	0	2 (1.0)	6 (3.1)
PPES	0	0	1 (0.5)	5 (2.6)	19 (9.9)	44 (22.9)
Pancreatitis	0	0	1 (0.5)	0	0	0
Peripheral edema	0	0	1 (0.5)	0	2 (1.0)	1 (0.5)
Pruritus	0	0	2 (1.0)	0	1 (0.5)	5 (2.6)
Pyrexia	1 (0.5)	1 (0.5)	8 (4.2)	0	0	5 (2.6)
Rash	1 (0.5)	1 (0.5)	2 (1.0)	1 (0.5)	2 (1.0)	15 (7.8)

RPED	0	5 (2.6)	8 (4.2)	0	0	1 (0.5)
Rhabdomyolysis	1 (0.5)	0	0	0	0	0
Transaminases increased	5 (2.6)	0	9 (4.7)	0	1 (0.5)	3 (1.6)
Uveitis	0	1 (0.5)	6 (3.1)	0	0	0
VTE	0	0	3 (1.6)	0	0	0
Visual impairment	0	0	3 (1.6)	0	0	0
Vomiting	0	0	13 (6.8)	3 (1.6)	1 (0.5)	9 (4.7)
Source: Reviewer generated table using ISS_ADADR (cutoff 9 May 2016, submitted by Applicant) **Abbreviations:** ALP = alkaline phosphatase; CPK = creatine phosphokinase; LV= left ventricular; PPES = palmar-plantar erythrodysesthesia; RPED = retinal pigment epithelial detachment; VTE = venous thromboembolism						

Adverse Reactions

The ADR and AESI analyses form the basis of the adverse reactions (ARs) identified by the applicant for inclusion in the labels for encorafenib and binimetinib. Table 72 summarizes the ARs associated with BRAF and MEK inhibitors currently labeled for use in patients with advanced or metastatic BRAF mutated melanoma. The BRAF inhibitors are: vemurafenib, which is approved as monotherapy and dabrafenib, which is approved as monotherapy or in combination with trametinib. The MEK inhibitors are cobimetinib, which is approved in combination with vemurafenib, and trametinib, which is approved as monotherapy or in combination with dabrafenib.

Table 73 summarizes the important safety signals for encorafenib and binimetinib as identified by the Applicant for inclusion in their proposed labels.

Individual ARs observed in COMBO 450 and/or other BRAF/MEK inhibitors that are considered “important,” “common,” and “otherwise clinically relevant” are discussed individually in more detail below. An “important” AR is one included in Section 5, Warnings and Precautions of a label; “common” ARs are those noted in Section 6.1 of a label and for COMBO 450 occurred in ≥ 25% of patients; “otherwise clinically relevant” ARs are also clinically notable but occur in < 10% of patients and are also noted in Section 6.1 of a label. This discussion focuses on TEAEs reported in COLUMBUS Part 1 Combo 450 and encorafenib arms and to assist with assessing contribution by each drug to the event the binimetinib monotherapy pool. For rare events, the Combo > 400 pooled dataset is evaluated. All analyses are performed regardless of investigator or Applicant attribution to study drug(s).

Table 72: Important Safety Issues with Related Drugs in Patients with BRAF Mutated Melanoma

	Warnings/Precautions	**Common Adverse Reactions**	**Clinically Relevant Adverse Reactions reported in < 10%**
Vemurafenib (Zelboraf) [1]	New Primary Malignancies Cutaneous Malignancies Non-Cutaneous Squamous Cell Carcinoma Other Malignancies Tumor Promotion in BRAF Wild-Type Melanoma Hypersensitivity Reactions Dermatologic Reactions: severe dermatologic reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis QT Prolongation Hepatotoxicity Photosensitivity Ophthalmologic Reactions: uveitis, blurry vision, photophobia Embryo-Fetal Toxicity Radiation Sensitization and Radiation Recall Renal Failure: acute interstitial nephritis and acute tubular necrosis Dupuytren's Contracture and Plantar Facial Fibromatosis	Arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma	Palmar-plantar erythrodysesthesia syndrome, keratosis pilaris, panniculitis, erythema nodosum, Steven-Johnson syndrome, toxic epidermal necrolysis, arthritis, Dupuytren's contracture, neuropathy peripheral, VIIth nerve paralysis, basal cell carcinoma, oropharyngeal squamous cell carcinoma, folliculitis, retinal vein occlusion, vasculitis, atrial fibrillation
Dabrafenib (Tafinlar) [2]	New Primary Cutaneous Malignancies Cutaneous Malignancies Non-Cutaneous Malignancies Tumor Promotion in BRAF Wild-Type Melanoma Hemorrhage Cardiomyopathy Uveitis Serious Febrile Reaction Serious Skin Toxicity Hyperglycemia G6PD Deficiency Embryo-Fetal Toxicity	<u>Single agent:</u> Hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmer-planter erythrodysesthesia syndrome <u>Given with trametinib</u> Pyrexia, rash, chills, headache, arthralgia, and cough	<u>Single agent:</u> Pancreatitis, hypersensitivity manifesting as bullous rash, interstitial nephritis <u>Given with trametinib</u> Pancreatitis, panniculitis,

	Warnings/Precautions	**Common Adverse Reactions**	**Clinically Relevant Adverse Reactions reported in < 10%**
Cobimetinib (Cotellic) [3]	New Primary Cutaneous Malignancies Cutaneous Malignancies Non-Cutaneous Malignancies Hemorrhage Cardiomyopathy Severe Dermatologic Reactions Serous Retinopathy and Retinal Vein Occlusion Hepatotoxicity Rhabdomyolysis Severe Photosensitivity Embryo-Fetal Toxicity	Diarrhea, photosensitivity reaction, nausea, pyrexia, and vomiting	pneumonitis
Trametinib (Mekinist)[4]	New Primary Cutaneous Malignancies Cutaneous Malignancies Non-Cutaneous Malignancies Hemorrhage Colitis and Gastrointestinal Perforation Venous Thromboembolism Cardiomyopathy Ocular Toxicities Renal Vein Occlusion Retinal Pigment Epithelial Detachment Interstitial Lung Disease Serious Febrile Reactions Serious Skin Toxicity Hyperglycemia Embryo-Fetal Toxicity	<u>Single agent:</u> rash, diarrhea, lymphedema <u>Given with Dabrafenib</u> Pyrexia, nausea, rash, chills, diarrhea, vomiting, hypertension, and peripheral edema	<u>Single agent:</u> Bradycardia, dry mouth, folliculitis, rash pustular, cellulitis, rhabdomyolysis, dizziness, dysgeusia, blurred vision, dry eye <u>Given with Dabrafenib</u> Bradycardia, rhabdomyolysis,

Table 73: Applicant Proposed Labeled Safety Issues: Encorafenib and Binimetinib

	Warnings/Precautions Section 5	Common Adverse Reactions (≥ 25%) Section 6.1	Clinically Relevant Adverse Reactions reported in < 10% Section 6.1	Drug Interaction
Encorafenib	New Primary Malignancies Cutaneous Malignancies Non-Cutaneous (b) (4) (b) (4) Hemorrhage (b) (4) uveitis Embryo-Fetal Toxicity	Fatigue, nausea, vomiting, arthralgias	Facial paresis, pancreatitis, panniculitis, drug hypersensitivity	Strong CYP3A4 Inhibitors Strong (b) (4) Inducers (b) (4)
Binimetinib	(b) (4) Cardiomyopathy Venous Thromboembolism Ocular Toxicities Serous retinopathy Retinal Vein Occlusion Uveitis Interstitial Lung Disease Hepatotoxicity Rhabdomyolysis Hemorrhage Embryo-Fetal Toxicities	Diarrhea, abdominal pain	Colitis, Drug hypersensitivity	(b) (4)

Source: Applicant proposed labels for encorafenib (BRATOVI) and binimetinib (MEKTOVI) submitted to the applications June 30, 2017.

Important ADRs and AESIs Identified in BRAF and MEK Inhibitors and in Combo 450

1. New Primary Malignancies

Cutaneous

Secondary skin neoplasms are a known known class effect of BRAF inhibitors. They are not reported as a class effect for MEK inhibitors. The secondary skin neoplasms associated with BRAF inhibitors include cutaneous squamous cell carcinoma (cuSCC) and cutaneous non-squamous cell carcinomas.

The ADR cutaneous squamous cell carcinoma (CuSCC) comprises keratoacanthoma, lip squamous cell carcinoma, and squamous cell carcinoma. The incidence of cuSCC in the COLUMBUS Part 1 encorafenib monotherapy was 7.8%. The incidence in the COLUMBUS Part 1 Combo 450 arm was more than 5% lower, at an observed rate of 2.6%. The incidence was extremely low in patients who received binimetinib alone (0.2%). All events in the patients receiving encorafenib with or without binimetinib in COLUMBUS Part 1 were ≤ Grade 2, and no cases were categorized as serious. In COLUMBUS Part 1 Combo 450 arm or the encorafenib monotherapy arm, there were no events of cutaneous squamous cell carcinoma that led to treatment discontinuation, dose interruption, and/or reduction.

The decrease in observed frequency of CuSCC observed when binimetinib is added to encorafenib is consistent what is observed with other combination regimens involving BRAF and MEK inhibitors.

The AESI of cutaneous non-squamous cell carcinomas comprises the following PTs: basal cell, neoplasm skin, and dysplastic nevus syndrome. The incidence in COLUMBUS Part 1 Combo 450 arm was 2.1% (1.6% basal cell) and in the encorafenib monotherapy arm was 1% (1% basal cell). Thus, the decrease in incidence of CuSCC with the addition of binimetinib to encorafenib is not recapitulated with non-squamous cutaneous neoplasms. In COLUMBUS Part 1 Combo 450 arm or the encorafenib monotherapy arm, there were no events of cutaneous non-squamous cell carcinoma that led to treatment discontinuation, dose interruption, and/or reduction.

Non-cutaneous

To determine the incidence of non-cutaneous malignancies, this Reviewer defined a grouped term “non-cutaneous malignancy” using all AEs that were included in an AEHLGT containing the word “malignant,” with the exception of skin neoplasms. In Columbus Part 1, the incidence of non-cutaneous malignancy was 1.0% in the Combo 450 arm (2/192) and 1.6% in the encorafenib monotherapy arm (3/192). One of the cases in the Combo 450 arm was squamous cell carcinoma (0.5%) while all three observed in the encorafenib monotherapy arm were squamous cell carcinoma. Of note, 16 patients in the vemurafenib arm had a non-cutaneous malignancy (8.6%) with 12 of these patients (6.5%) having squamous cell carcinoma.

The ADR new primary malignancies, both cutaneous and non-cutaneous, is included in Warnings and Precautions for the vemurafenib, dabrafenib, cobimetinib, and trametinib labels. [redacted] (b) (4) Although non-cutaneous malignancies in general, and non-cutaneous squamous cell carcinoma in particular, are rare in patients who received Combo 450 or encorafenib monotherapy in the COLUMBUS

Part 1 trial, the Applicant proposes the inclusion of non-cutaneous malignancies in Warnings and Precautions based on the mechanism of action of encorafenib and the general risk for it to promote the growth and development of malignancies associated with activation of RAS.

2. Cardiomyopathy

Cardiomyopathy is a known class effect associated with BRAF inhibitors and MEK inhibitors.

Based on AE reporting in COLUMBUS Part 1, the incidence of the ADR left ventricular dysfunction in the Combo 450 arm is 7.8% (1.6% Grade 3, 0% Grade 4) and in the encorafenib monotherapy arm is 2.1 % (1% Grade 3-4). No AEs were reported as serious.

The incidence of left ventricular dysfunction, however, is more accurately assessed based on ECHO/MUGA reporting. As discussed in Section 8.2.3 and shown in Table 67, the Combo 450 regimen resulted in a higher proportion of patients experiencing a worsening of LVEF as measured by ECHO/MUGA compared to the encorafenib monotherapy or vemurafenib arms. A similar increase in Grade 2 toxicity is observed when comparing the Combo 300 arm with the encorafenib 300 monotherapy arm in COLUMBUS Part 2. This data suggests that the increased toxicity observed in the Combo 450 arm is due to the addition of binimetinib rather than the increase in dose of encorafenib. In COLUMBUS Part 1, no patients in the Combo 450 arm and 2 patients in the encorafenib monotherapy arm (1%) discontinued treatment due to left ventricular dysfunction. Twelve patients in the Combo 450 arm (6.3%) and no patients in the encorafenib monotherapy arm interrupted treatment because of left ventricular dysfunction. No patient in either arm had a dose reduction for left ventricular dysfunction. Cardiomyopathy is labeled in Warnings and Precautions for dabrafenib, cobimetinib, and trametinib. It is not included in the label for vemurafenib. (b) (4)

3. *Hepatotoxicity*

Hepatotoxicity, including elevation of hepatic enzymes, is a known class effect associated with BRAF and MEK inhibitors. Hepatotoxicity was identified as an AESI for binimetinib based on a case of fatal liver failure in Study CMEK162X2201 in which the patient developed acute liver failure after receiving a dose of binimetinib 60 mg BID.

Based on AE reporting, 13.5% of patients in Columbus Part 1 COMBO 450 arm and 6.8% of patients in the encorafenib monotherapy arm had a PT that fell under the Applicant-defined ADR Transaminase Increased [1]. None of these events were serious. Five patients (2.6%) in the Combo 450 arm and 2 patients (1%) in the encorafenib monotherapy arm discontinued therapy due to increased transaminases. Nine patient (4.7%) in the Combo 450 arm and 3 patients (1.6%) in the encorafenib monotherapy arm had a dose interruption. No patients in the Combo 450 arm and 1 patient (0.5%) in the encorafenib monotherapy had a dose reduction for the ADR transaminase increased. In the Combo 450 arm, 13 patients (6.8%) had a Grade 3 event while in the encorafenib monotherapy arm, 3 patients (1.6%) had a Grade 3 event. No patient

[1] The ADR Transaminase Increased includes the PTs alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased.

on either arm had a Grade 4 event. In COLUMBUS Part 1, 5 patients in the Combo 450 arm (2.6%) and 4 patients in the encorafenib monotherapy arm (2.1%) discontinued treatment due to the ADR transaminases increased. No patients in the Combo 450 arm and 1 patient in the encorafenib monotherapy arm (0.5%) had a dose reduction for this ADR. There were 9 patients in the Combo 450 arm (4.7%) and 3 patients in the encorafenib monotherapy arm (1.6%) who had a dose interruption.

In the binimetinib monotherapy pooled dataset, the incidence of the ADR increased transaminase was 16.6% (71/427) with 3% of patients having a Grade 3 event. No Grade 4 events were reported. Only 2 patients (0.5%) had events that were reported as serious.

Hepatotoxicity may also be evaluated based laboratory assessments. As seen in Table 64, in COLUMBUS Part 1, significantly more patients in the Combo 450 arm experienced an increase in ALT (29%), AST (27%), ALP (21%), and GGT (45%) than in the encorafenib monotherapy arm (ALT: 15%, AST 12%, ALP: 14%, GGT: 37%). The majority of events for both arms were Grade 1 and 2. In the Combo 450 arm, 6% of patients had a Grade 3-4 increase in ALT, 2.6% a Grade 3-4 increase in AST, 0.5% a Grade 3-4 increase in ALP, and 12% a Grade 3-4 increase in GGT. In the encorafenib monotherapy arm, 1.6% experienced a Grade 3-4 increase in ALT, 0.5% a Grade 3-4 increase in AST, 0% a Grade 3-4 increase ALP, and 9.4% of patients a Grade 3-4 increase in GGT. There were no cases meeting the criteria for Hy's law in the Combo 450 or Part 1 encorafenib monotherapy arms.

While a significant portion of patients in the Combo 450 arm experienced increases in transaminases, the increase was usually mild (≤ Grade 2) and did not lead to a serious AE. Both encorafenib and binimetinib appear to contribute to the hepatotoxicity observed with Combo 450; however, based on the totality of the data, the contribution of binimetinib appears greater.

Hepatotoxicity is listed in Warnings and Precautions in the vemurafenib (as liver injury) and cobimetinib (as liver laboratory abnormalities) but not the dabrafenib or trametinib product labels. (b) (4)

4. Hemorrhage

Hemorrhage is a known class effect associated with MEK inhibitors.

In COLUMBUS Part 1, hemorrhage occurred in 18.8% of patients in the Combo 450 arm (13% Grade 1, 2.6% Grade 2, 1.6% Grade 3, and 1.6% Grade 4) and in 10.9% of patients in the encorafenib monotherapy arm (7.3% Grade 1, 1.6% Grade 2, and 1.0% Grade 3, and 1.0% Grade 4. In the Combo 450 arm, the most frequent hemorrhagic events were gastrointestinal (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%). In COLUMBUS Part 1, 3 patients in the Combo 450 arm (1.6%) and no patients in the encorafenib monotherapy arm discontinued treatment due to the ADR hemorrhage. No patients in either the Combo 450 or encorafenib monotherapy arm had a dose reduction, while 2 patients in the Combo 450 arm (1.0%) and 2 patients in the encorafenib monotherapy arm (1.0%) had an event that led to treatment interruption.

In the binimetinib pooled population, hemorrhage was reported in 9.8% of patients.

Hemorrhage includes the PT cerebral hemorrhage. In the Combo 450 arm, 1.6% (3/193) had a fatal cerebral hemorrhage. One additional patient in the Combo 450 arm was reported as having intracranial tumor hemorrhage (0.5%). In Part 1 encorafenib arm, 2 patients (1.0%) had a fatal intracranial hemorrhage. Although these events were considered related to new cerebral metastasis, COLUMBUS does not provide information that allows assessment if Combo 450 or encorafenib monotherapy increases this risk.

Hemorrhage is included in Warnings and Precautions in the dabrafenib but not the vemurafenib label and in the cobimetinib and trametinib labels. The Applicant proposes the inclusion of hemorrhage in Warnings and Precautions of the encorafenib and the binimetinib labels.

5. Ocular Toxicities

After Amendment 3 to the COLUMBUS protocol, ophthalmic examinations including slit lamp examination, visual acuity, intraocular pressure (IOP), and fundoscopy were required for all enrolled patients. Patients on the Combo 450 and Combo 300 arms as well as patients on the encorafenib monotherapy and vemurafenib arms with baseline retinal abnormalities had ophthalmic examinations during screening, at each regulatory scheduled patient visit (Day 1 of each cycle), EOT, and at the 30-day safety follow-up. Ophthalmic Coherence T (OCT) (for non-vascular abnormalities) and/or fluorescein angiography (for vascular abnormalities) examinations were required for patient with clinical findings indicative of retinal abnormalities.

(b) (4)

DOP 2 requested an ophthalmology consult from the Division of Transplant and Ophthalmology Products (DTOP) to review the risks of ocular events in patients receiving binimetinib in combination with encorafenib. Three ocular events were reviewed based on known class effects of BRAF and MEK inhibitors: retinopathy excluding retinal vein occlusion (RVO), RVO, and uveitis.

Retinopathy is a known class effect of MEK inhibitors. Clinical findings are characterized by serous retinal detachment. In COLUMBUS Part 1, retinopathy, excluding RVO events, was reported in a higher percentage of patients in the Combo 450 arm (48.4%) as compared with the encorafenib monotherapy (13.5%) and vemurafenib arms (12.4, %). This was true for all PTs included in the term retinopathy.

The incidence of the narrower ADR RPED for Columbus Part 1 Combo 450 arm was 19.8% (38/192) and in the encorafenib monotherapy arm was 2.1% (6/192). In the Combo 450 arm, symptomatic RPED (Grade ≥ 2 in the Applicant's grading system) was noted in 15 patients (7.8%) and in 1 patient in the encorafenib monotherapy arm (0.5%). For 38 patients in the Combo 450 arm (19.8%) and 6 patients in the encorafenib monotherapy arm (3.1%) the event was serious. No patients on either arm discontinued treatment due to RPED. In the Combo 450 arm, 5 patients (2.6%) and no patients in the encorafenib arm required dose reduction. There were 8 patients in the Combo 450 arm (4.2%) and 1 patient in the encorafenib monotherapy arm 0.5%) who interrupted treatment due to RPED.

The incidence of RPED in the pooled binimetinib monotherapy arm was 35.4%. Based on the data, the serous retinopathy observed in patients who receive Combo 450 is due to the binimetinib.

Retinopathy is included Warnings and Precautions in the cobimetinib label as serous retinopathy and the trametinib label as RPED. Retinopathy is not included in the vemurafenib or dabrafenib labels. The Applicant proposes the inclusion of serous retinopathy in Warnings and Precautions of the binimetinib label.

Retinal vein occlusion is a known class effect of MEK inhibitors. Based on the low frequency, the Applicant does not include it as a separate ADR. It was, however, evaluated as an AESI. In COLUMBUS Part 1, no RVO events were reported in any patient in the Combo 450 or in the larger pooled dataset COMBO > 400. One patient in the Columbus Part 1 encorafenib monotherapy arm (0.5%) experienced RVO. The event was grade 3 and no action was taken with treatment.

In the binimetinib monotherapy pooled dataset, 9 patients experienced RVO for an incidence of 2.1%. Five patients (1.2%) had Grade 3-4 events. Seven of the patients (1.6%) discontinued treatment due to RVO. One of the 7 patients had previously had a dose adjustment or interruption for Grade 1 event that subsequently progressed to Grade 2 before discontinuation.

Although not observed in patients receiving binimetinib with encorafenib, based on the single agent binimetinib data along with experience with other MEK inhibitors, the Applicant considers RVO an adverse reaction associated with binimetinib.

RVO is included in Warnings and Precautions in the cobimetinib and trametinib labels only. The Applicant proposes the inclusion of serous retinopathy in Warnings and Precautions of the binimetinib label.

Uveitis is a known class effect of BRAF inhibitors. In COLUMBUS Part 1, the ADR uveitis occurred in 3.6% of patients in the Combo 450 arm and only 0.5% of patients in the encorafenib monotherapy arm. Uveitis did not lead to discontinuation in any patients in COLUMBUS Part 1. Uveitis led to dose reduction in 1 patient (0.5%) and dose interruption in 6 patients (3.1%) in the Combo 450 arm while no patients in the encorafenib monotherapy arm had a dose interruption or reduction due to uveitis.

Uveitis is generally associated with BRAF inhibitors rather than MEK inhibitors. In the vemurafenib arm from Part 1 of Columbus, the incidence was 3.8%. The data from COLUMBUS in which the incidence of uveitis in patients receiving encorafenib monotherapy was low (0.7% across Parts 1 and 2) but was higher in patients receiving encorafenib with binimetinib (3.6% in the Combo 450, 3.9% in Combo 300) suggests that the primary contributor to toxicity is binimetinib. This is, however, inconsistent with the incidence of uveitis in the binimetinib monotherapy pooled dataset where the incidence was 0.2%. There is no clear explanation for the low rate of uveitis observed in the encorafenib monotherapy arm. One might postulate that is it artifact due to closer ophthalmologic monitoring required for patients receiving combination therapy; however, the incidence in the vemurafenib arm was 3.8%. One might postulate that it is related to the lower dose of encorafenib in the monotherapy arm; however, the incidence of uveitis in COLUMBUS Part 2 Combo 300 arm (3.9%) was similar to that

observed in the Combo 450 arm. Overall, based on the data, uveitis is assessed as related to both encorafenib and binimetinib.

Uveitis is included Warnings and Precautions in the vemurafenib and dabrafenib labels only and not included in the cobimetinib and trametinib labels. The Applicant proposes the inclusion of uveitis to Warnings and Precautions of the encorafenib and binimetinib labels.

6. Venous Thromboembolism

Venous thromboembolism (VTE) is a know class effect of MEK inhibitors. In COLUMBUS, the ADR VTE occurred in 5.7% (11/192) of patient in the Combo 450 arm (1.6% Grade 3-4) and in 3.1% of patients in the encorafenib monotherapy arm (1% Grade 3-4). In the Combo 450 arm, 3.1% of the patients had a serious VTE event. No patients in the encorafenib monotherapy event had a serious VTE event. No patients in the Combo 450 arm discontinued therapy due to the event of VTE while 1 patient (0.5%) required a dose reduction and 6 patients (3.1%) required dose interruption. No patient in the encorafenib monotherapy arm discontinued, reduced, or interrupted therapy due to VTE. The ADR VTE occurred in 4.4% of patients in the binimetinib monotherapy pooled dataset.

Based on the data, VTE is assessed as related to the binimetinib in the Combo 450 regimen.

Venous thromboembolism is included Warnings and Precautions in the trametinib label. The Applicant proposes the inclusion of venous thromboembolism to Warnings and Precautions of the binimetinib label.

7. Interstitial Lung Disease (ILD)

Interstitial lung disease/pneumonitis is a known class effect associated with MEK inhibitors. The AESI pneumonitis, used by the Applicant, comprises the PT Interstitial lung disease, lung infiltration, and pneumonitis. In COLUMBUS 0.5% of patients in the Combo 450 arm and 1% of patients in the encorafenib monotherapy arm experienced ILD. No additional cases were observed in the Combo ≥ 400 pooled dataset (0.2%). In the binimetinib monotherapy pooled dataset there were 6 patients with ILD (1.4%), with 2 of the patients having Grade 3 events (0.5) (no Grade 4 events), and 3 patients having events categorized as serious.

ILD is rare in patients receiving Combo 450. ILD is included in Warnings and Precautions in the trametinib label. It is noted in other clinical experience in the combimetinib label (pneumonitis). The Applicant proposes inclusion of the ADR interstitial lung disease in Warnings and Precautions of the binimetinib label.

8. *Rhabdomyolysis*

Elevation of serum CPK is a known class effect associated with MEK inhibitors. It may be associated with muscular symptoms. Rhabdomyolysis is not included in the label for vemurafenib or dabrafenib. It is included in Warnings and Precautions in the cobimetinib label. It is included with other clinically important adverse reactions (Section 6.1) in the trametinib label.

A higher percentage of patients in the Combo 450 arm (58%) compared with the encorafenib monotherapy part 1 arm (3%) and the vemurafenib arm (3.8%) had elevated laboratory value of

CPK. In the Combo 450 arm, 5% of patients had Grade 3 laboratory CPK elevation (all Grade 3) while no patients on the encorafenib monotherapy arm had Grade 3-4 laboratory CPK elevation. No patients in either arm had Grade 4 toxicity.

Despite the high number of patients who experienced Grade 1-2 CPK elevation, rhabdomyolysis was reported in only 1 patient in the Combo 450 arm (0.5%). No additional cases were observed in the Combo ≥ 400 pool (0.2%).

Based on AE reporting, 1 patient on the Combo 450 arm discontinued treatment due to elevated CPK with 6 patients (3.1%) requiring treatment interruption. No patients in the encorafenib monotherapy arm discontinued, reduced, or interrupted treatment due to elevated CPK or rhabdomyolysis.

The incidence in the binimetinib monotherapy pooled safety set was 0.5% (2 patients). All cases were Grade 3-4. No cases of rhabdomyolysis were reported in the encorafenib monotherapy part 1 or the vemurafenib arms.

The applicant reports that in the Combo 450 arm, of the patients who had an elevation of laboratory values of serum CPK, seven (6.3%) had at least one temporally associated muscle-related AE reported. The patient who experienced rhabdomyolysis had Grade 4 laboratory CPK elevation, muscle symptoms, and renal dysfunction.

Rhabdomyolysis is included in Warnings and Precautions in the cobimetinib label. It is noted with other clinically important adverse reactions under Clinical Experience in the trametinib label. Rhabdomyolysis is not included in the vemurafenib or dabrafenib labels. The Applicant proposes inclusion of rhabdomyolysis in the binimetinib label but not the encorafenib label.

9. QT prolongation

As seen in Table 66 from Section 8.2.3, while 27% of patients in the Combo 450 arm and 29% in of patients in the encorafenib monotherapy arm have an increased in QTcF more than 30 ms, few patients have a more significant increased of more than 60 ms with only 5.4% patients in the Combo 450 arm and 3.9% of patient in the encorafenib monotherapy arm experiencing such a change. Similarly, while 14% of patients in the Combo 450 arm have a new QTcF > 450 ms (21 % in the encorafenib monotherapy arm), a new QTcF > 500ms was rare in the Combo 450 arm with only 0.5% of patients having such an event (2.8% in the encorafenib monotherapy arm. Thus, mild increases were common, a larger, more serious increases, were rare. No patients discontinued treatment because of QT prolongation.

QT prolongation is included in Warnings and Precautions for the vemurafenib label. It is noted in the dabrafenib label under Pharmacodynamics that “no large changes in the mean QT interval (i.e., > 20 ms) were detected with dabrafenib 300 mg administered twice daily (two times the recommended dosage).” QT prolongation is not included in the cobimetinib or the trametinib labels.

As discussed in Section 8.2.3, QT-IRT found no large QTc prolongation (20 ms) is expected following a dose of 45 mg BID for binimetinib while a dose dependent QTc interval prolongation is associated with encorafenib.

The Applicant did not include QTc as an adverse reaction in either the encorafenib or binimetinib label; however, based on the QT-IRT, FDA believes QTc prolongation should be included in Warnings and Precautions in the encorafenib label. This is consistent with the safety analysis as well as the Applicant's proposed dose modifications for prolonged QTc, and is discussed further in Section 11.

Additional Common (≥ 25%) ADRs Observed in Combo 450

10. Fatigue

The ADR fatigue is commonly reported for patients on all arms in the Columbus Trial. In part 1, 43.2% of patients in the Combo 450 arm (3.1% Grade 3-4) and 41.7% of patients in the encorafenib monotherapy arm (3.1% Grade 3-4) experienced fatigue. Despite its frequency, only 2 patients (1%) in the Combo 450 arm and in the encorafenib monotherapy arm had events that were categorized as serious. One patient in the Combo 450 arm (0.5%) and no patients in the encorafenib monotherapy arm discontinued therapy because of fatigue. In the Combo 450 arm, 4 patients (2.1%) required treatment interruption while 2 patients (1.0%) required dose reduction. In the encorafenib monotherapy arm, 9 patients (4.7%) required treatment interruption and 4 patients (2.1%) required treatment reduction.

The addition of binimetinib in the Combo 450 arm did not increase the incidence of fatigue, although the incidence of fatigue in the binimetinib pooled dataset was 40%.

11. Nausea

The ADR nausea is commonly reported for patients on all arms in the Columbus Trial. In part 1, 41.1% of patients in the Combo 450 arm (1.6% Grade 3-4) and 38.5% of patients in the encorafenib monotherapy arm (4.2% Grade 3-4) experienced nausea. Despite its frequency, only 2 patients (1%) in the Combo 450 arm and 6 patients (3%) in the encorafenib monotherapy arm had events that were categorized as serious. No patients in either arm discontinued therapy because of nausea. In the Combo 450 arm, 14 patients (7.3%) required treatment interruption because of nausea while 2 patients (0.5%) required dose reduction. In the encorafenib monotherapy arm, 11 patients (5.7%) required treatment interruption and 6 patients (3.1%) required treatment reduction.

The addition of binimetinib in the Combo 450 arm did not increase the incidence of nausea, although the incidence of nausea in the binimetinib pooled dataset was 30%.

12. Vomiting

The ADR vomiting is commonly reported for patients on all arms in the Columbus Trial. In Part 1, 29.7% of patients in the Combo 450 arm (1.6% Grade 3-4) and 27.1% of patients in the encorafenib monotherapy arm (4.7% Grade 3-4) experienced vomiting. Despite its frequency, only 3 patients (1.6%) in the Combo 450 arm and 6 patients (3%) in the encorafenib monotherapy arm had events that were categorized as serious. No patients in the Combo 450 arm and 3 patients (1.6%) in the encorafenib monotherapy arm discontinued therapy because of vomiting. In the Combo 450 arm, 13 patients (6.8%) required treatment interruption because

of vomiting and no patients required dose reduction. In the encorafenib monotherapy arm, 9 patients (4.7%) required dose interruption and 1 patient (0.5%) required treatment reduction.

The addition of binimetinib in the Combo 450 arm did not increase the incidence of vomiting, although the incidence in the binimetinib monotherapy pooled dataset was 19.7%.

13. Arthralgias

The ADR arthralgias is commonly reported for patients on all arms in the Columbus Trial. In Part 1, 25.5% of patients in the Combo 450 arm (0.5% Grade 3-4) and 44.3% of patients in the encorafenib monotherapy arm (9.4% Grade 3-4) experienced arthralgias. Despite its frequency, no patients in the Combo 450 arm and only 1 patients (0.5%) in the encorafenib monotherapy arm had events that were categorized as serious. No patients in the Combo 450 arm and 1 patients (0.5%) in the encorafenib monotherapy arm discontinued therapy because of arthralgias. In the Combo 450 arm, 3 patients (1.6%) required treatment interruption because of arthralgias with 1 (0.5%) patients requiring dose reduction. In the encorafenib monotherapy arm, 16 patients (8.3%) required dose interruption and 8 patients (4.2%) required treatment reduction.

Although the incidence of arthralgias in the binimetinib monotherapy pooled dataset was 7.5%, the addition of binimetinib to encorafenib decreases the incidence in the Combo 450 arm. This is consistent with what is observed in other MEK/BRAF regimens and suggests some of the arthralgia observed with encorafenib is related to activation of the RAS pathway.

14. Diarrhea

The ADR diarrhea is frequently reported for patients on all arms in the Columbus Trial. In Part 1, 36.5% of patients in the Combo 450 arm (2.6% Grade 3-4) while only 13.5% of patients in the encorafenib monotherapy arm (1.6% Grade 3-4) experienced diarrhea. Despite the frequency of diarrhea AEs, only 1 patient (0.5%) in the Combo 450 arm and in the encorafenib monotherapy arm had an event that was categorized as serious. One patient in the Combo 450 arm (0.5%) and 2 patients (1.0%) in the encorafenib monotherapy arm discontinued therapy because of diarrhea. In the Combo 450 arm, 6 patients (3.1%) required treatment interruption and 1 patient (0.5%) requiring dose reduction for diarrhea. In the encorafenib monotherapy arm, 4 patients (2.1%) required dose interruption and no patients required dose reduction.

The incidence of diarrhea in the binimetinib monotherapy pooled dataset was 42.6%. The addition of binimetinib to encorafenib in the Combo 450 arm increases the incidence of diarrhea, although serious events and events leading to discontinuation or dose reduction remain rare.

15. Abdominal Pain

The ADR abdominal pain is frequently reported for patients on all arms in the Columbus Trial. In Part 1, 28.2% of patients in the Combo 450 arm (3.6% Grade 3-4) while only 16.7% of patients in the encorafenib monotherapy arm (3.1% Grade 3-4) experienced abdominal pain. It is notable that 6 patients (3.1%) in the Combo 450 arm and 4 patients (2.1%) in the encorafenib monotherapy arm had an event that was categorized as serious.

In the Combo 450 arm 6 patients (3.1%) and 4 patients (1.0%) in the encorafenib monotherapy arm discontinued therapy because of abdominal pain. In the Combo 450 arm, 6 patients (3.1%) required treatment interruption and 1 patient (0.5%) requiring dose reduction for abdominal pain. In the encorafenib monotherapy arm, 6 patients (3.2%) required dose interruption and 1 patient (0.5%) patient required dose reduction.

The incidence of abdominal pain in the binimetinib monotherapy pooled dataset was 15.9%. The addition of binimetinib to encorafenib in the Combo 450 arm increases the incidence of abdominal pain, and in both the Combo 450 and the encorafenib monotherapy arms, a relatively high number of patients discontinued therapy because of this ADR.

Clinically Relevant Adverse Reactions Reported in < 10% COMBO 450

16. Facial Paresis

Facial paresis has been reported in patients receiving BRAF inhibitors. In COLUMBUS Part 1, the incidence of facial paresis in the Combo 450 arm and vemurafenib arms was 1.0%. In the encorafenib arm, the incidence was 7.3% (1.6% Grade 3-4). In the encorafenib monotherapy arm, facial paresis was reported as an SAE for 2.6% of patients, led to discontinuation in 1% of patients, and required dose interruption and/and or change in 3.6% of patients. Facial paresis was not reported in any patients in the binimetinib pooled dataset. The addition of binimetinib effectively eliminates this toxicity in patients receiving Combo 450.

Facial paresis has been observed in patients receiving vemurafenib. The vemurafenib label notes VIIth nerve paralysis under clinically relevant adverse reactions (Section 6.1) reported in < 10% of patients. Similarly, the Applicant proposed label for encorafenib includes the AR facial paresis in Section 6.1 under clinically relevant adverse reactions reported in < 10% Combo 450.

17. Pancreatitis

Pancreatitis is a known class effect associated with BRAF inhibitors. In the Combo 450 arm Grade 3-4 AEs of amylase and lipase elevations were reported in 1.6% and 1.6% of patients. The Applicant reports that a clinical review showed in 4 patients in the Combo 450 arm elevation was associated with abdominal pain, two of whom were diagnosed with acute pancreatitis. While the ADR pancreatitis occurred in 2 patients in the Combo 450 arm (1%), there were no patients in the encorafenib monotherapy arm with the ADR pancreatitis. There were 2 cases of pancreatitis in the Combo 450 arm that were categorized as serious. No patients discontinued or reduced treatment for pancreatitis. One patient (0.5%) interrupted treatment because of pancreatitis.

In the binimetinib monotherapy pooled population, there were no cases of pancreatitis.

Pancreatitis is included in the dabrafenib label under clinically relevant adverse reactions (Section 6.1) reported in < 10% of patients. The Applicant proposed label for encorafenib includes the AR pancreatitis in Section 6.1 under clinically relevant adverse reactions reported in < 10% Combo 450.

18. Panniculitis

Panniculitis is associated with use of BRAF and MEK inhibitors. In COLUMBUS Part 1, the ADR panniculitis occurred in 1.6% of patients (0% Grade 3-4) in the Combo 450 arm and 0.5% of patients in the encorafenib monotherapy arm. No patient in the Combo 450 or encorafenib arms discontinued, reduced, or interrupted therapy due to panniculitis. In the binimetinib monotherapy pooled dataset, panniculitis occurred in 0.2% of patients.

Panniculitis is included in the vemurafenib and dabrafenib labels under clinically relevant adverse reactions (Section 6.1) reported in < 10% of patients. The Applicant proposed label for encorafenib includes the AR panniculitis in Section 6.1 under clinically relevant adverse reactions reported in < 10% Combo 450.

19. *Drug Hypersensitivity*

The ADR drug hypersensitivity comprises the events urticaria, angioedema, hypersensitivity, hypersensitivity vasculitis, cutaneous vasculitis, vasculitis, and drug eruptions. In COLUMBUS Part 1, The ADR drug hypersensitivity occurred in 3.6% of patients in the Combo 450 arm (0% Grade 3-4) and in 4.7% of patients in the encorafenib monotherapy arm (0.5% Grade 3-4). One patient in the Combo 450 a5m (0.5%) and 1 patient in the encorafenib monotherapy arm (0.5%) had a drug hypersensitivity event that was classified as serious. No patients in the Combo 450 arm discontinued, reduced, or interrupted therapy due to drug hypersensitivity event. In the encorafenib monotherapy arm, 2 patients (1%) discontinued, 2 patients (1%) reduced, and 3 patients (1.6%) interrupted therapy due to drug hypersensitivity.

In the binimetinib monotherapy pooled population, 1.2% of patients had a drug hypersensitivity event.

Drug hypersensitivity is in Warnings and Precautions of the vemurafenib label and under clinically relevant adverse reactions (Section 6.1) reported in < 10% of patients in the dabrafenib label. The Applicant proposed labels for encorafenib and binimetinib include the AR drug hypersensitivity in Section 6.1 under clinically relevant adverse reactions reported in < 10% Combo 450.

20. Colitis

The ADR colitis comprises the events colitis, colitis ulcerative, enterocolitis, proctitis.

In COLUMBUS Part 1, the ADR colitis occurred in 2.1% of patients (1% Grade 3-4) in the Combo 450 arm and 1.0% of patients in the encorafenib monotherapy arm (0% Grade 3-4). Two patients in the Combo 450 arm (1%) had events that were classified as serious. No patients in the encorafenib arm had events classified as serious. No patient in the Combo 450 arm or the encorafenib monotherapy arm discontinued treatment due to colitis. In the Combo 450 arm, 1 patient (0.5%) reduced treatment while 2 patients (1%) interrupted treatment due to colitis. In the encorafenib monotherapy arm, no patients reduced treatment and 1 patient (0.5%) interrupted treatment due to colitis. There were no reports of intestinal perforation in the Combo 450 or encorafenib arms.

In the binimetinib monotherapy pooled dataset, there were no patients with the ADR colitis reported.

Colitis and Intestinal Perforation is included in Warnings and Precaution for the trametinib label. The Applicants proposed label for binimetinib include the AR colitis in Section 6.1 under clinically relevant adverse reactions reported in < 10% Combo 450.

Important ARs Identified in BRAF and MEK Inhibitors but not included in the proposed binimetinib or encorafenib labels

21. Severe Cutaneous Reactions

Serious cutaneous reactions are known to occur with BRAF and MEK inhibitors. Severe or serious dermatologic reactions are included in Warnings and Precautions in the vemurafenib, dabrafenib, cobimetinib, and trametinib labels. The Applicant did not include Severe Cutaneous Reactions in the set of ADRs due to the low frequency in the Combo 450 arm (1 patient), but did assess the events as an AESI.

The incidence in patients receiving encorafenib and/or binimetinib is low. All cases reported in COLUMBUS Part 1 were reported under the PT exfoliative dermatitis. Across the pooled combination dataset, there was one additional patient with an event of toxic skin eruption. In the pooled binimetinib dataset, 5 patients (1.2%) had a serious cutaneous reaction.

No AEs of Stevens Johnson Syndrome or toxic epidermal necrolysis occurred in the Combo ≥ 400, binimetinib monotherapy, or encorafenib monotherapy datasets.

The Applicant does not propose inclusion of serious cutaneous reactions in Warnings and Precautions for the binimetinib label.

22. Photosensitivity

Photosensitivity is an adverse drug reaction known to be associated with vemurafenib and is included in Warnings and Precautions in the vemurafenib and cobimetinib labels.

The AESI photosensitivity comprises the PTs of photosensitivity reaction, solar dermatitis, and dermatitis. In COLUMBUS Part 1, 5.2% of patients (10/192) in the Combo 450 arm, 4.7% of patients in the encorafenib monotherapy arm, and 37.6% of patients (70/186) in the vemurafenib arm had the AE of photosensitivity. The majority of events in patients receiving encorafenib with or without binimetinib were Grade 1 or 2. In the larger Combo ≥ 400 pooled dataset, 3.5% of patients experienced a photosensitivity event. The risk of photosensitivity associated with encorafenib or Combo 450 regimen is low.

The Applicant does not propose inclusion of photosensitivity in the labels for binimetinib or encorafenib.

23. Radiation Sensitization and Radiation Recall

Radiation sensitization and radiation recall has been observed in patients taking vemurafenib and based on post marketing experience was added as a Warnings and Precaution to the label. In the ISS dataset submitted to binimetinib and encorafenib applications, there were no reports of radiation sensitization or radiation recall. In COLUMBUS Part 1, there was only 1 report of radiation injury in the Combo 450 arm (0.5%).

The applicant does not propose inclusion of radiation sensitization and/or recall in the labels for binimetinib or encorafenib.

24. Renal Failure

Renal Failure has been associated with use of BRAF inhibitors. It is included in Warnings and Precautions in the Vemurafenib label and as interstitial nephritis with other clinically important adverse reactions in Section 6.1 of the dabrafenib label.

The AESI acute renal failure includes the following PTs: acute kidney injury, renal failure, renal impairment, and oliguria. In COLUMBUS Part 1, 3.6% of patients in the Combo 450 arm (2.6% Grade 3-4), 2.6% of patients in the encorafenib monotherapy arm (1.6% Grade 3-4), and 4.8% of patients in the vemurafenib arm (1.6% Grade 3-4) had an AE classified as acute renal failure. Acute renal failure led to discontinuation of therapy in no patients in the Combo 450 arm and in 2 patients (1.0%) in the encorafenib monotherapy arm. The incidence of the AESI acute renal failure in the Combo ≥400 pooled dataset was 3.5% (2.1% Grade 3-4), similar to the that observed in the combination arm in COLUMBUS Part 1.

Considering laboratory measurement of creatinine as a marker of renal impairment, in COLUMBUS Part 1, 92.7% of patients in the Combo 450 arm (3.6% Grade 3-4) and 76.6% of patient in the encorafenib monotherapy arm (0.5% Grade 3-4) had a post baseline abnormal creatinine measure. Therefore, it appears that the addition of binimetinib or the increased dose of encorafenib may have increased the incidence of creatinine increases slightly in the Combo 450 patients; however, this may also be due to the longer exposure observed in the Combo 450 arm. Mild increases in creatinine can occur in cancer patients in the absence of drug therapy. In the absence of a placebo control arm, it is difficult to determine drug effect based on Grade 1 elevations. In summary, while increased creatinine was common in the COLUMBUS trial, Grade 3-4 increases were not.

The applicant does not propose inclusion of acute renal failure or any renal related AR in the binimetinib or encorafenib labels.

25. Dupuytren's Contracture and Plantar Facial Fibromatosis

Dupuytren's contracture, also known as plantar facial fibromatosis, is slowly progressive fibrosis of the palmar fascia, has been observed in patients who have received vemurafenib and is postulated as an adverse reaction associated with the BRAF inhibitor. Although not included in the original label for vemurafenib, Dupuytren's contracture was subsequently added. In the ISS dataset submitted to binimetinib and encorafenib applications, there were no reports of Dupuytren's contracture or plantar fascial fibromatosis. This reviewer examined all TEAEs classified in the SOC Musculoskeletal and connective tissue disorders to identify possible case with none found.

The applicant does not propose inclusion of Duputren's Contracture and Plantar Facial Fibromatosis in the binimetinib or encorafenib labels.

26. Serious Febrile Reaction

Serious febrile reactions have been observed in patients treated with dabrafenib as a single agent or administered with trametinib and is included in Warnings and Precautions for both

labels. The ADR pyrexia comprises the PTs body temperature increased, hyperpyrexia, hyperthermia, and pyrexia. In COLUMBUS Part 1, 18.2% of patients in the Combo 450 arm (4.2% Grade 3-4), 15.6% of patients in the encorafenib monotherapy arm (1% Grade 3-4), and 29.6% of patients in the vemurafenib arm (0% Grade 3-4) had an event classified as the ADR pyrexia. In the Combo 450 arm, there were no Grade 4 events. Pyrexia led to discontinuation of treatment in 0.5% and interruption or reduction of dose in 4.2%.

The PT pyrexia was the most commonly reported SAE in Combo 450 arm of COLUMBUS occurring in 6 patients (3.1%). Review of the narratives for these patients reveals that 2 patients developed an SAE of pyrexia after discontinuation of treatment due to progressive disease. Pyrexia resolved in both patients. Two patients developed an SAE of pyrexia associated with concurrent infections. One patient developed an SAE of pyrexia which resolved the next day without intervention. One patient had multiple episodes of pyrexia, one of which was classified as an SAE. No infectious etiology was identified and the events were not associated with concurrent AEs associated with infections. In summary 4 of the 6 patients had concurrent factors which may have contributed to the pyrexia, resulting in 2 patients in the Combo 450 arm (1%) having the AE pyrexia considered serious for which there is not an identifiable cause other than study drug.

The applicant does not propose inclusion of serious febrile reaction in the binimetinib or encorafenib labels.

27. Hyperglycemia

Hyperglycemia is included in Warnings and Precautions for the dabrafenib and trametinib labels.

In COLUMBUS Part 1, the incidence of the PT blood glucose increased was 1.6% in the Combo 450 arm (0.5% Grade 3-4) and 0% in the encorafenib monotherapy arm. None of the events were categorized as serious and no events required treatment discontinuation, interruption, or reduction. In the binimetinib monotherapy pooled dataset, there was only 1 patients (0.2%).

For hyperglycemia based on laboratory assessment, 27.6% of patients in the Combo 450 arm (5.2% Grade 3-4) and 27.1% of patients in the encorafenib monotherapy Part 1 arm (4.2%) had an increased fasting glucose (change from baseline).

The applicant does not propose inclusion of hyperglycemia in the binimetinib or encorafenib labels.

28. G6PD Deficiency

G6PD deficiency is included in Warnings and Precautions for the dabrafenib label. Encorafenib contains a sulfonamide moiety; however, the applicant does not include this potential risk in Warnings and Precautions in the proposed label. In response to an IR from FDA (dated 2/2/2008), the applicant provided an assessment of risk of hemolytic anemia for patients with G6PD. Key points are copied from the submission (SDN0024 submitted 2/5/2018) below:

- *Risk assessment for hemolytic anemia in patients with G6PD deficiency is based on ADME data showing that despite the sulfonamide moiety in the molecule,*

metabolism of encorafenib does not produce reactive metabolites associated with hemolysis in patients with G6PD and clinical data from across the clinical program for encorafenib did not show any cases of hemolytic anemia.

- *In vitro and in vivo ADME data from monkeys and humans confirm that encorafenib metabolism does not produce glutathione adducts of N-acetyl cysteine adducts. Thus, the hallmarks of reactive metabolites are not present following administration of encorafenib to humans and non-human primates.*

Attenuation of encorafenib associated ADRs by binimetinib

Table 74 shows the ADRs in which the frequency was a least 5% lower in the COMBO 450 compared to the encorafenib monotherapy arm. The attenuation of BRAF toxicities with the addition of a MEK inhibitor has been observed in other regimens that use BRAF and MEK inhibitors together. It is postulated that these toxicities are the result of a paradoxical activation of MAP kinase signally in BRAF wild-type cells by the BRAF inhibitor while the MEK inhibitor blocks this effect. In other BRAF/MEK combination regimens, this effect has been observed primarily in skin associated toxicities including hyperkeratosis, cuSCC, alopecia, and PPES. The list of ADRs in which the combination therapy is less toxic than encorafenib monotherapy include several toxicities not reported for other BRAF/MEK combination regimens.

The label for encorafenib should indicate the increased risk for these ADRs if a patient must discontinue binimetinib. Further, based on dose finding trials, the dose of encorafenib should be decreased to 300 mg once daily.

Table 74: ADRs Decreased (≥5%) in Combo 450 arm compared to Encorafenib monotherapy arm: COLUMBUS Part 1

ADR	Combo 450 N=192 All grades % (Grade 3-4 %)	Enc 300 N=192 All grades % (Grade 3-4 %)	Combo 450-Enc 300 Δ Incidence All Grades (Grade 3-4)
PPES	6.8 (0)	51 (13.5)	-44.3 (-13.5)
Alopecia	14.1 (-)	56.3 (-)	-42.2 (-)
Hyperkeratosis	22.9 (0.5)	57.3 (4.7)	-34.4 (-4.2)
Dry skin	16.1 (-)	37.5 (-)	-21.4 (-)
Arthralgia	25.5 (0.5)	44.3 (9.4)	-18.8 (-8.9)
Rash	22.4 (1.0)	41.1 (4.2)	-18.7 (-3.1)
Pruritus	12.5 (0.5)	30.7 (0.5)	-18.2 (0)
Pain in extremity	10.9 (1.0)	21.9 (1.0)	-10.9 (9)
Neuropathy	12 (1.0)	21.9 (1.0)	-9.9 (0)
Myopathy	23.4 (0)	33.3 (9.9)	-9.9 (-9.9)
Erythema	7.3 (0)	15.6 (1.6)	-8.3 (-1.6)

ADR	Combo 450 N=192 All grades % (Grade 3-4 %)	Enc 300 N=192 All grades % (Grade 3-4 %)	Combo 450-Enc 300 Δ Incidence All Grades (Grade 3-4)
Dysgeusia	5.7 (-)	13 (-)	-7.3 (-)
Facial paresis	1 (0.5)	7.3 (1.6)	-6.3 (-1.0)
Headache	21.9 (1.6)	28.1 (3.6)	-6.3 (-2.1)
Back pain	9.4 (0.5)	15.1 (2.6)	-5.7 (-2.1)
CuSCC	2.6 (0)	7.8 (0)	-5.2 (0)
Acneiform dermatitis	3.1 (0)	8.3 (0)	-5.2 (0)
Source: Reviewer generated table using ISS_ADADR (cutoff 9 May 2016, submitted by Applicant) **Abbreviations:** cuSCC = cutaneous squamous cell carcinoma, PPES = palmar-plantar erythrodysesthesia.			

Combo 450 versus Combo 300

In COLUMBUS Part 2, patients were randomized to received Combo 300 or encorafenib 300mg monotherapy. Although Part 1 and Part 2 were randomized at separate times, the demographics and baseline characteristics between the groups are similar, allowing an exploratory comparison of safety. Table 75 provides a comparison of overall safety between the Combo 450 and Combo 300 arm in COLUMBUS. Overall, the two arms are similar in: median exposure, on treatment deaths, and incidence of adverse events with the following exceptions: patients in the Combo 450 arm had a higher incidence of Grade 3-4 AEs (58%) compared to patients in the Combo 300 arm (47%), patients in the Combo 450 arm had a higher incidence of serious AEs (34%) compared to patients in the Combo 300 arm (29%), and patient in the Combo 450 arm had a higher incidence of Grade 3-4 AEs requiring dose interruption (33%) compared to patients in the Combo 300 arm (23%). For other parameters, the difference in incidence was < 5% between the two arms.

Table 76 lists ADRs that occur with increased frequency (≥5%) in the Combo 450 arm when compared to the Combo 300 arm.

In summary, the increased dose of encorafenib used in the Combo 450 arm compared to the Combo 300 arm results in a slight increase in toxicity, but this increase in toxicity does not lead to greater number of on treatment deaths or discontinuations. It does lead to slight increase in severity of adverse events.

Table 75: Summary of Deaths and Adverse Events Combo 450 versus Combo 300: COLUMBUS

	Combo 450 N=192 Median duration of exposure 51.21 weeks		Combo 300 N=257 Median duration of exposure 52.14 weeks	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)

On-treatment deaths (≤ 30 days EOT)	17 (8.9)	----	25 (9.7)	---
Adverse Events	189 (98.4)	111 (57.8)	252 (98.1)	120 (46.7)
Serious AEs	66 (34.4)	57 (29.7)	75 (29.2)	65 (25.3)
AEs leading to discontinuation	24 (12.5)	22 (11.5)	32 (12.5)	23 (8.9)
AE requiring dose interruption/reduction	92 (47.9)	63 (32.8)	115 (44.7)	59 (23.0)

Source: CSR COLUMBUS Part 1 Table 35, CSR COLUMBUS Part 2 Initial Table 24.

Table 76: ADRs increased (≥5%) in Combo 450 arm versus Combo 300 arm: COLUMBUS

ADR	Combo 450 N=192 % All Grades (% Gr 3-4)	Combo 300 N=257 % All Grades (% Gr 3-4)
Nausea	43.2 (1.6)	27.2 (1.6)
Vomiting	30.2 (1.6)	15.2 (0.4)
Hemorrhage	19.3 (3.6)	6.6 (1.6)
Fatigue	45.3 (3.1)	33.5 (1.6)
Headache	22.9 (1.6)	12.1 (0.4)
Rash	22.9 (1.0)	14 (0.8)
Diarrhea	37.0 (2.6)	28.4 (1.6)

Source: Reviewer generated table using ISS_ ADADR (Submitted with 4-month safety update 10/27/2018)

8.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no COA analyses performed informing safety and tolerability. Patient reported outcomes are not included in the label. An analysis of COA as a secondary or exploratory endpoint is discussed in Section **Error! Reference source not found..**

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8.2.6. Safety Analyses by Demographic Subgroups

TEAES by Age

Table 77 summarizes AEs by age group for COLUMBUS Part 1. Patients were categorized as < 65 years of age or ≥ 65 years of age. In the COMBO 450 arm, a higher proportion of older patients (≥ 65 years) experienced Grade 3-4 TEAEs and SAEs and this translated into higher proportion of patients having a TEAE leading to reduction and/or interruption of treatment. Analysis comparing the frequency of individual ADRs in patients < 65 years of age to the frequency in patients ≥ 65 years of age identified some minor differences; however, some differences are to be expected due to chance alone, and given the limited number of patients in each group, a true interaction between gender and these differences could not be concluded. While adverse events occur more frequently in patients ≥ 65 years, this is observed across all treatment arms

and is unlikely to be treatment-specific. Furthermore, age ≥ 65 does not result in an increased frequency of treatment interruption or discontinuation. Therefore, no age specific labeling is indicated.

Table 77: Overall Summary of Adverse Events by Age Group: COLUMBUS Part 1

Event	COLUMBUS Part 1					
	Combo 450		Enc 300		Vem	
	<65 N= 132 n (%)	≥65 N= 60 n (%)	<65 N= 153 n (%)	≥65 N= 39 n (%)	<65 N= 136 n (%)	≥65 N=50 n (%)
Any TEAE	129 (97.7)	60 (100)	153 (100)	38 (97.4)	135 (99.3)	50 (100)
Grade 3-4 TEAE	73 (55.3)	38 (63.3)	99 (64.7)	28 (71.8)	83 (61.0)	35 (70)
Any SAE	42 (31.9)	24 (40.0)	51(33.3)	14 (35.9)	53 (39.0)	16 (32.0)
Grade 3-4 SAE	36 (27.3)	21 (35.0)	43 (28.1)	11 (28.2)	46 (33.8)	14 (28.0)
TEAE leading to discontinuation	16 (12.1)	8 (13.3)	21 (13.7)	6 (15.4)	18 (13.2)	13 (26.0)
TEAE leading to interruption	59 (44.8)	29 (48.3)	98 (64.0)	24 (61.5)	71 (52.2)	27 (54.0)
TEAE leading to reduction	11 (0.8)	11 (18.3)	42 (27.4)	10 (25.6)	26 (19.1)	16 (32.0)
TEAE leading to interruption/reduction	60 (45.5)	32 (53.3)	109 (71.2)	26 (66.7)	80 (58.8)	34 (68.0)

Source: Reviewer generate table ISS_ADAE (cutoff 9 May 2016, submitted by applicant)

TEAES by Gender

Table 78 summarizes the adverse events by sex for COLUMBUS Part 1. Across all stages, 60% of patients diagnosed with melanoma will be male. This ratio was maintained generally across arms in the trial. The incidence for each event e.g., Grade 3-4 TEAE, is similar (≤10% difference) between male and female patients for each arm. Analysis comparing the frequency of individual ADRs in males to the frequency in females did identify some minor differences; however, given the limited number of patients in each group, a true interaction between gender and these differences could not be concluded. Therefore, no gender specific labeling is indicated.

Table 78: Overall Summary of Adverse Events by Sex: COLUMBUS Part 1

Event	COLUMBUS Part 1					
	Combo 450		Enc 300		Vem	
	Male N= 115 n (%)	Female N= 77 n (%)	Male N= 106 n (%)	Female N= 86 n (%)	Male N= 108 n (%)	Female N= 78 n (%)
Any TEAE	112 (97.4)	77 (100)	105 (99.1)	86 (100)	107 99.1)	78 (100)

Event	COLUMBUS Part 1					
	Combo 450		Enc 300		Vem	
	Male N= 115 n (%)	Female N= 77 n (%)	Male N= 106 n (%)	Female N= 86 n (%)	Male N= 108 n (%)	Female N= 78 n (%)
Grade 3-4 TEAE	65 (56.6)	46 (59.7)	73 (68.9)	54 (62.8)	67 (62.0)	51 (65.4)
Any SAE	42 (36.5)	24 (31.2)	43 (40.6)	22 (25.6)	41 (38.0)	28 (35.9)
Grade 3-4 SAE	37 (32.3)	20 (26.0)	33 (31.1)	21 (24.4)	34 (31.5)	26 (33.3)
TEAE leading to discontinuation	9 (7.8)	5 (6.5)	5 (4.7)	5 (5.8)	7 (6.5)	4 (5.1)
TEAE leading to interruption	20 (17.4)	7 (9.1)	20 (18.9)	13 (15.1)	14 (13.0)	11 (14.1)
TEAE leading to reduction	3 (2.6)	0	0	1 (1.2)	2 (1.9)	0
TEAE leading to interruption/reduction	22 (19.1)	7 (9.1)	20 (18.9)	14 (16.3)	15 (13.9)	11 (14.1)

Source: Reviewer generate table ISS_ADAE (cutoff 9 May 2016, submitted by applicant)

8.2.7. Specific Safety Studies/Clinical Trials

No clinical trials were conducted to evaluate a specific safety concern. As covered in Section 8.2.3 with the discussion of QT, while a dedicated QT trial was not performed, three cardiac studies were submitted.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See Section 5.5.3.

Human Reproduction and Pregnancy

There were no reported exposures to encorafenib or binimetinib in pregnant or lactating women.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No AEs of overdose have been reported for patients receiving single-agent encorafenib or single agent binimetinib. One SAE report of an overdose of binimetinib was reported for a patient receiving binimetinib given with encorafenib. The patient was prescribed to take 45 mg twice daily of binimetinib along with 300 mg once daily of encorafenib. Approximately 6.5 months after starting treatment, the patient took a one time 135 mg dose of binimetinib while omitting the encorafenib dose. No AEs were reported with the overdose event. The event was considered resolved after 5 days.

In dose escalation trials of encorafenib to be given with a fixed dose of 45 mg twice daily of binimetinib, patients received encorafenib 600 mg QD (68 patients) and 800 mg (6 patients). Per the Applicant, the most commonly reported AEs in patients receiving doses ≥ 600 mg were nausea, diarrhea, fatigue, constipation, abdominal pain, vomiting, headache, and arthralgia. In addition, 21% of patients receiving doses ≥ 600 mg had events of renal dysfunction (Grade 3 hypercreatinemia).

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application. Safety with long-term use of encorafenib and binimetinib when used together will need to be monitored closely given the risk of secondary malignancies associated with RAS pathway activation by encorafenib.

8.2.10. Integrated Assessment of Safety

The evaluation of the safety of the Combo 450 regimen in patients with locally advanced or metastatic melanoma with a BRAF V600 E/K mutation was based primarily on the 570 patients randomized in COLUMBUS Part 1 who received at least one dose of study drug(s). Part 1 of COLUMBUS was a randomized, open label, multi-center, controlled trial comparing the efficacy and safety of encorafenib plus binimetinib versus vemurafenib versus encorafenib monotherapy in patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation. Of the 570 patients, 192 received encorafenib plus binimetinib (Combo 450), 192 patients received encorafenib monotherapy, and 186 patients received vemurafenib.

The review also included analysis of a pooled dataset of 433 patients who received encorafenib ≥ 400 mg QD in conjunction with binimetinib 45 mg BID. This pooled dataset was considered adequate to detect serious but rare events associated with the regimen.

COLUMBUS excluded patients that were at increased risk of adverse reactions from the known toxicity of kinase inhibitors of BRAF and/or MEK. Such inclusion criteria included the following:

- History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyper viscosity or hypercoagulability syndromes);
- Impaired cardiovascular function or clinically significant cardiovascular diseases, including history of acute coronary syndromes (including myocardial infarction, unstable angina, CABG, coronary angioplasty, or stenting) <6 months prior to screening, symptomatic chronic heart failure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality <6 months prior to screening;

- Uncontrolled hypertension despite medical treatment;
- Patients who have neuromuscular disorders that are associated with elevated CPK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

In COLUMBUS, the median duration of exposure to Combo 450 regimen was 51.2 weeks (range 0.4 weeks to 116 weeks) with 52.6% of patients receiving the combination treatment for at least 48 months. Table 79 summarizes the overall safety profile of the Combo 450 regimen as observed in COLUMBUS Part 1. Overall the Combo 450 regimen was generally better tolerated than vemurafenib with lower incidence of Grade 3-4 TEAEs, SAEs, AEs leading to discontinuations and lower incidence of AEs leading to reductions or interruptions, despite a longer median exposure in the Combo 450. Tolerability of Combo 450 was similar to that observed in the encorafenib monotherapy arm.

Table 79: Summary of Safety Events: COLUMBUS Part 1

Category	Combo 450 N=192 n (%)	Enc 300 N=192 n (%)	Vemurafenib N=186 n (%)
Median Exposure (weeks)	51.2	31.4	27.1
On-treatment deaths[1]	17 (8.9)	14 (7.3)	19 (10.2)
Adverse Event	189 (98.4)	191 (99.5)	185 (99.5)
Grade 3-4	111 (57.8)	127 (66.1)	118 (63.4)
Serious Adverse Event	66 (33.4)	65 (33.9)	69 (37.1)
Grade 3-4	57 (29.7)	54 (28.1)	60 (32.3)
AE → discontinuation	24 (12.5)	27 (14.1)	31 (16.7)
Grade 3-4	22 (11.5)	21 (10.9)	18 (9.7)
AE → dose interruption/ change	92 (47.9)	135 (70.3)	114 (61.3)
Grade 3-4	63 (32.8)	85 (44.3)	71 (38.2)

[1] Includes deaths due to disease progression
Source: Reviewer generated table – summarizing Review Tables

The most common adverse drug reactions observed in the Combo 450 arm, occurring in at least 20% of patients, were: fatigue, nausea, diarrhea, vomiting, abdominal pain, arthralgias, myopathy, hyperkeratosis, headache, rash constipation, RPED, and visual impairment. In addition, Grade 3-4 laboratory abnormalities observed in at least 5% of patients in the Combo 450 arm were increased ALT, increased AST, increased fasting glucose, and increased GGT. Other serious but rare adverse drugs reactions include: new cutaneous malignancies such as squamous cell cutaneous squamous cell carcinoma, left ventricular dysfunction, hemorrhage with a risk of cerebral hemorrhage associated with brain metastases, retinal pigment epithelial detachment, uveitis, retinal vein occlusion, venous thromboembolism, interstitial lung disease, rhabdomyolysis, and QT prolongation.

Overall, the safety profile of the Combo 450 regimen is similar to that observed with other BRAF/MEK inhibitor regimens, including the commonly observed adverse drug reactions as well as the rare but serious toxicities. No new safety signals were identified in the course of this review. As with other BRAF/MEK regimens, there is a risk of several toxicities, including secondary malignancies, associated with RAS pathway activation due to a BRAF inhibitor, specifically encorafenib. As with other BRAF/MEK regimens, this toxicity is attenuated by the addition of a MEK inhibitor, specifically binimetinib. With Combo 450, however, this attenuation affect appears to apply to a larger set of toxicities than observed in other BRAF/MEK inhibitor combinations, for example arthralgias and myalgias/myopathy.
The safety profile of the Combo 450 regimen for the treatment of patients with advanced or metastatic BRAF V600 mutant melanoma is acceptable with adverse reactions typically managed through temporary treatment discontinuation or dose reduction.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

COLUMBUS was not adequately designed to demonstrate that the efficacy of Combo 450 is superior to Combo 300 for any endpoint. Because Part 1 and Part 2 were randomized at different times, comparisons of Combo 450 to Combo 300 may not be meaningful. However, results from Parts 1 and 2 do not suggest any detrimental effect of Combo 450 vs. Combo 300 on key efficacy endpoints.

COLUMBUS failed to demonstrate a statistically meaningful difference in PFS between Combo 450 and encorafenib. However, estimates of the treatment effect suggest Combo 450 may increase PFS when compared to encorafenib. This comparison does not account for differences in dosing. Part 2 of COLUMBUS was designed to isolate the effect of binimetinib, as encorafenib was given at 300mg in both arms. Estimates from Part 2 of the treatment effect of Combo 300 vs. encorafenib on PFS suggest that Combo 300 increases PFS, although this comparison was not pre-specified as the primary analysis of this comparison. The test pre-specified to assess this comparison, Test 3, utilized patients from both Parts 1 and 2, and consequently may be biased. However, the results from Test 3 also suggest a treatment effect of Combo 300 on PFS when compared to encorafenib.

8.4. Conclusions and Recommendations

COLUMBUS demonstrated that the combination regimen of encorafenib 450 mg once daily given with binimetinib 45 mg twice daily had a statistically significant effect on PFS when compared to vemurafenib, with estimated median PFS times of 14.9 months (95% CI: [11.0, 18.5]) for the Combo 450 arm and 7.3 months (95% CI: [5.6, 8.2]) for the vemurafenib arm, along with an associated hazard ratio of 0.54 (95% CI: [0.41, 0.71]). The risks identified with the use of the combination regimen were consistent with other BRAF/MEK inhibitor regimens and are manageable by medical oncologists.

Based on the favorable risk: benefit profile, the clinical and statistical reviewers recommend approval for binimetinib and encorafenib when given together for patients with advanced or metastatic melanoma harboring a BRAF V600 mutation.

Jonathan Vallejo, PhD Primary Statistical Reviewer	Lisa Rodriguez, PhD Statistical Team Leader
Margaret Thompson, MD, PhD Primary Clinical Reviewer	Ashley Ward, MD Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this NDA.

10 Pediatrics

Encorafenib and binimetinib were not studied in pediatric patients. Encorafenib with binimetinib was granted orphan designation status for the treatment of Stage IIB-IV melanoma positive for the BRAF mutation on 11/19/2013 (Orphan Designation Number 13-4116).

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Encorafenib (BRAFTOVI)

The following are recommended major changes to the BRAFTOVI (encorafenib) prescribing information proposed by the applicant based on this review:

- **1 INDICATIONS AND USAGE:**
  Add Limitation of Use stating that BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma as required per 21 CFR 201.57, which states that if evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), include a succinct description of the limitations of usefulness of the drug.
- **2 DOSAGE AND ADMINISTRATION:**
  Modify Dosage Modifications for Adverse Reactions as follows:
  - Include exceptions to dose modifications of BRAFTOVI for those ARS associated with binimetinib as a footnote to Table 2.
  - Remove (b) (4)

  Add Section 2.4 Dose Modifications for Coadministration of Strong or Moderate CYP3A4 Inhibitors providing the recommended dose reductions for patient who cannot avoid concomitant use of these drugs.
- **5 WARNINGS AND PRECAUTIONS (W&P)**
  - In general:
    - Except for rare events of those attenuated by the addition of binimetinib, a W&P should include only the incidence for encorafenib given with binimetinib. (b) (4)
  - Add new W&P Tumor Promotion in BRAF Wild-Type Tumors as this serious effect has been shown with other BRAF inhibitors.
  - (b) (4)
  - Add "QTc Prolongation" as a new W&P based on the observed QTc changes in patients in the COLUMBUS trial and the assessment that this toxicity is due to encorafenib. Array disagreed with FDA's proposal to add QTc prolongation to W&P, presenting their argument in a letter submitted to the NDA on 5/25/2018 (SDN 34). A teleconference subsequently occurred between Array and FDA on June 6, 2018 to discuss this disagreement.

In their letter, Array argued that the observed effect in terms of central tendency is best described by data from the Week 2 Day 1 time point or from an average of all time points that encompass the steady-state data, both of which showed an upper-bound 90% CI < 20 ms for mean QTc change. They stated that the former represents the steady-state value with the lowest variability, and the latter incorporates all available data. This is in contrast to FDA, whose assessment used 6-week data and is consistent with the intersection-union test recommended in the context of thorough studies in the ICH E14 guidance.

Array further stated that the absence of any clinical signal and the low observed rate of clinically relevant QTc prolongations > 500 ms suggests a limited potential for clinically meaningful arrythmogenic effects. While Array acknowledged a signal for concentration-dependent QTc prolongation, they maintain that the effect is below the threshold that would warrant inclusion in W&P.

At the teleconference, Array restated their belief that the inter-subject variability of QTC effect is high, and the effect of encorafenib on mean QTc change is less than 20 ms at encorafenib steady-state exposure.

FDA disagreed, considering the effect size as derived in the review by QT-IRT to be robust with similar effect size to that observed in another study with encorafenib monotherapy. FDA cited ICH E14, which states that a warning/precautionary statement should be recommended for drugs that prolong the QT/QTc interval (prolongation exceeds 5 ms as evidenced by an upper bound of the two sided 90% CI around 10 ms), and noted its general position, in the absence of a “definitive” QT study that can exclude a large QTc prolongation signal, is to require a QT prolongation Warnings and Precaution for an oncology drug based on the totality of evidence. It is the standard practice for FDA to base labeling recommendations on the largest upper bound of the two sided 90% CI for the by-time (central tendency) analysis.

With this additional explanation, Array agreed to include the W&P, and FDA agreed that only patients at high risk of QT prolongation at baseline needed to be monitored with serial ECG.

- Add “Risks associated with BRAFTOVI as a Single Agent” as a new W&P to warn that BRAFTOVI when used as a single agent is associated with an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with binimetinib.
- Add “Risks associated with Combination Treatment” as a new W&P to refer the clinician to the binimetinib label.

- **6 ADVERSE REACTIONS**
  - In Table 3, delete [redacted] and add information about adverse reactions that are observed at a higher rate in patients receiving BRAFTOVI alone compared to those receiving it in combination with binimetinib. During labeling negotiations, Array provided adequate justification for exclusion from Table 3 of AEs that could reasonably be attributed primarily or exclusively to binimetinib.
  - In Table 4, remove [redacted]. During labeling negotiations, Array provided adequate justificatio [redacted]
- **8 USE IN SPECIFIC POPULATIONS**
  - As per 21 CFR 21.57(c)9(v) remove data regarding geriatric use given clinical studies of encorafenib did not include sufficient number of patients aged 65 and older to determine whether they respond differently from younger patients.
- **12 CLINICAL PHARMACOLOGY**
  - **12.2 Pharmacodynamics:** Replace Array's proposal with the following text:
    Cardiac Electrophysiology
    A dedicated study to evaluate the QT prolongation potential of BRAFTOVI has not been conducted. BRAFTOVI is associateded with dose-dependent QTc interval prolongation. Following administration of the recommended dose of BRAFTOVI in combination with binimetinib, based on a central tendency anbalysis of QTc in a study of adult patients with melanoma, the largest mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (14 to 22) ms *[see Warnings and Precaution (5.5)].*
- **14 CLINICAL STUDIES**
  - Remove [redacted]
  - In Table 5, remove [redacted] add information for progressive disease and deaths, and calculate DOR for confirmed responses only.

<u>Binimetinib (MEKTOVI)</u>

The following are recommended major changes to the MEKTOVI (binimetinib) prescribing information proposed by the applicant based on this review:

- **2 DOSAGE AND ADMINISTRATION:**
  Modify Dosage Modifications for Adverse Reactions as follows:
  - Remove [redacted]
  - Add dose modifications for uveitis given its inclusion in W&PAdd Section 2.3 Dose Modifications for Moderate or Severe Hepatic Impairment
- **5 WARNINGS AND PRECAUTIONS (W&P)**

- Remove (b) (4)
- Cardiomyopathy: The incidence of this toxicity should be report as a decrease in ejection fraction based on ECHO or MUGA rather than left ventricular dysfunction based on adverse event reporting as the former provides a more accurate representation of the toxicity.

- **6 ADVERSE REACTIONS**
  - In Table 3, delete (b) (4) During labeling negotiations, Array provided adequate justification (b) (4)
  - In Table 4, remove (b) (4) During labeling negotiations, Array provided adequate justification (b) (4) FDA agreed that Table 4 does not need to be identical in the labels for BRAFTOVI and MEKTOVI.
- **8 USE IN SPECIFIC POPULATIONS**
  - As per 21 CFR 21.57(c)9(v) remove data regarding geriatric use given clinical studies of encorafenib did not include sufficient number of patients aged 65 and older to determine whether they respond differently from younger patients.
- **14 CLINICAL STUDIES**
  - Remove (b) (4)
  - In Table 5, (b) (4)

CDTL Comment: During labeling negotiations with the applicant, it was agreed that the rare but serious events of Retinal Vein Occlusion and Interstitial Lung Disease should be included in the Warnings & Precautions section of the binimetinib label (see rationale provided in Section 8.2.4 of this review). As these events were not observed in the primary safety pool (n=192 who received Combo 450 regimen on COLUMBUS), the applicant and the FDA agreed to use a pool of n=690 patients with BRAF V600 mutation positive melanoma who were exposed to binimetinib at a dose of 45 mg twice daily in combination with encorafenib at doses between 300 mg and 600 mg once daily across multiple clinical trials (COLUMBUS Parts 1 and 2, LOGIC2, and patients on Study CMEK162X2110 who received either the Combo 450 or the Combo 600 regimen) to describe the frequency of these events.

To ensure that patients are adequately informed of the risks of encorafenib and binimetinib and when to seek medical attention, the FDA requested that Array provide a Patient Medication Guide for encorafenib and a Patient Package Insert (PPI) for binimetinib. The FDA determined that a Patient Medication Guide was warranted for encorafenib due to the risk of new primary malignancies and the need for ongoing surveillance. The FDA determined that a PPI was sufficient to communicate the risks of binimetinib.

Carton and Container Labeling was reviewed per FDA standard practice. Numerous minor modifications were recommended to improve clarity and usability. See CMC, OPDP, DMEPA, and Patient Labeling review for details.

12 Risk Evaluation and Mitigation Strategies (REMS)

There are no safety issues identified that require Risk Evaluation and Mitigation Strategies (REMS).

13 Postmarketing Requirements and Commitment

A clinical postmarketing commitment was requested to provide mature overall survival data from COLUMBUS for the purposes of updating the product label. See action letter for final wording and milestone dates.

14 Division Director (DHOT)

John Leighton, PhD

15 Division Director (OCP)

Nam Atiqur Rahman, PhD

16 Division Director (OB)

Rajeshwari Sridhara, PhD

17 Associate Division Director (Clinical)

Steven Lemery, MD, MHS

18 Office Director

Richard Pazdur, MD

19 Appendices

19.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): CMEK162B2301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2146		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): CLGX818X2109

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 243		
Number of investigators who are Sponsor employees (including both full-time and part-time		

employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): CLGC818X2101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 194		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____		

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.2. OCP Appendices (Technical documents supporting OCP recommendations)

19.2.1. Population PK Aanalysis

The goal of population PK analysis (popPK) in this submission is to develop a population pharmacokinetic (PK) model to assess sources of variability (intrinsic and extrinsic covariates) and predict exposures to binimetinib, AR00426032 (active metabolite) and encorafenib. PopPK analyses were conducted by the applicant with Phoenix WinNonlin. Independent popPK analyses were conducted by the reviewer to confirm and reproduce the results using NONMEN 7.3.

19.2.1.1 Binimetinib

The popPK models for binimetinib and its active metabolite AR00426032 were developed sequentially. The parent drug model was developed first and extended to active metabolite by fixing individual post-hoc binimetinib PK parameters estimates. This review will focus on the parent drug model because abundance of the equipotent active metabolite is substantially lower than (<20%) that of the parent drug and hence is not considered the driving factor for efficacy or safety.

The popPK analysis included 428 patients contributing a total of 3128 binimetinib concentrations, among whom 192 (54.6%) were cancer patients enrolled in the Part 1 of the COLUMBUS trial. Majority of the binimetinib concentrations were collected at cycle 1 day 1 (35.6%) and cycle 1 day 15 (21.0%).

A two-compartment model with first-order absorption was found to best describe the PK profile of binimetinib. An Emax function to describe the time-varying CL was incorporated into this model to evaluate the potential magnitude and time-dependent effect of enzyme auto-induction. Interim population PK analysis was first conducted based on rich concentration-time profiles in study ARRAY-162-105 and CMEK162X2110. Same base model was applied to all

studies including sparse sampling in CMEK162B2301 Part 1 after fixing typical value of Emax and T50 to the estimates obtained in the interim analysis. Covariates were initially screened using visual inspection, and the most relevant covariates were formally evaluated within the population PK model using a full model approach. The full covariate model included the following covariates effects: time effect, gender, disease status (healthy subjects), hepatic impairment (NCI criteria), ECOG status, phase of clinical trial and combination therapy as categorical covariates, and creatinine clearance, albumin, bilirubin, body weight and age as continuous variables on CL/F, and age, body weight and albumin as continuous variable and gender and disease status as categorical variables on V/F. The final population PK parameters of binimetinib derived with the full covariate model were presented in Table 80. No signs of model misspecification were identified in the goodness-of-fit plots of full covariate model (Figure 18). The prediction-corrected visual predictive check (Figure 19) showed the model provided satisfactory prediction of the central tendency and variability of the observed data in both cycle 1 day 1 and cycle 1 day 15. An Emax function successfully describes the time-varying CL which was estimated to increase 0.84-fold at steady state with T50 at 81.3 hours.

The effect of evaluated covariates on binimetinib PK parameters were illustrated in the forest plot (Figure 17). Covariate effects indicate that extreme body weight values (5th and 95th percentiles) of approximately 52 and 111 kg were associated with within 20% differences in CL/F relative to a typical patient (78 kg). Consistent with the assumption that patients would exhibit relatively poor hepatic function compared to healthy subjects, CL/F was approximately 44% lower in patients relative to healthy subjects. Bilirubin levels, a marker for hepatic function, suggest an inverse relationship whereby the CL/F of binimetinib decreased with higher bilirubin levels, which was aligned with the results shown in the dedicated study. Patients with moderate or severe hepatic impairment should reduce the dose to 30 mg BID.

Evaluable binimetinib PK data in patients in Part 2 of study CMEK162B2301 was also added to the analysis dataset in order to obtain accurate post-hoc PK parameters to calculate predicted exposure metrics. The GOF plots in patients enrolled in Part 1 and Part 2 of study CMEK162B2301 were provided in Figure 20. The prediction-corrected visual predictive check for binimetinib PK profile in study CMEK162B2301 (Figure 21) confirms that model captured the observed PK profile of binimetinib and can be used to derive exposure metrics for the subsequent exposure-response analyses.

Final population PK models were used to derive rich concentration-time profiles at steady state and exposure metrics were derived according to the randomized dose of patients enrolled in the study. Summary of exposure metrics of binimetinib in patients enrolled in the COLUMBUS study Part 1 and Part 2 were presented in Table 81.

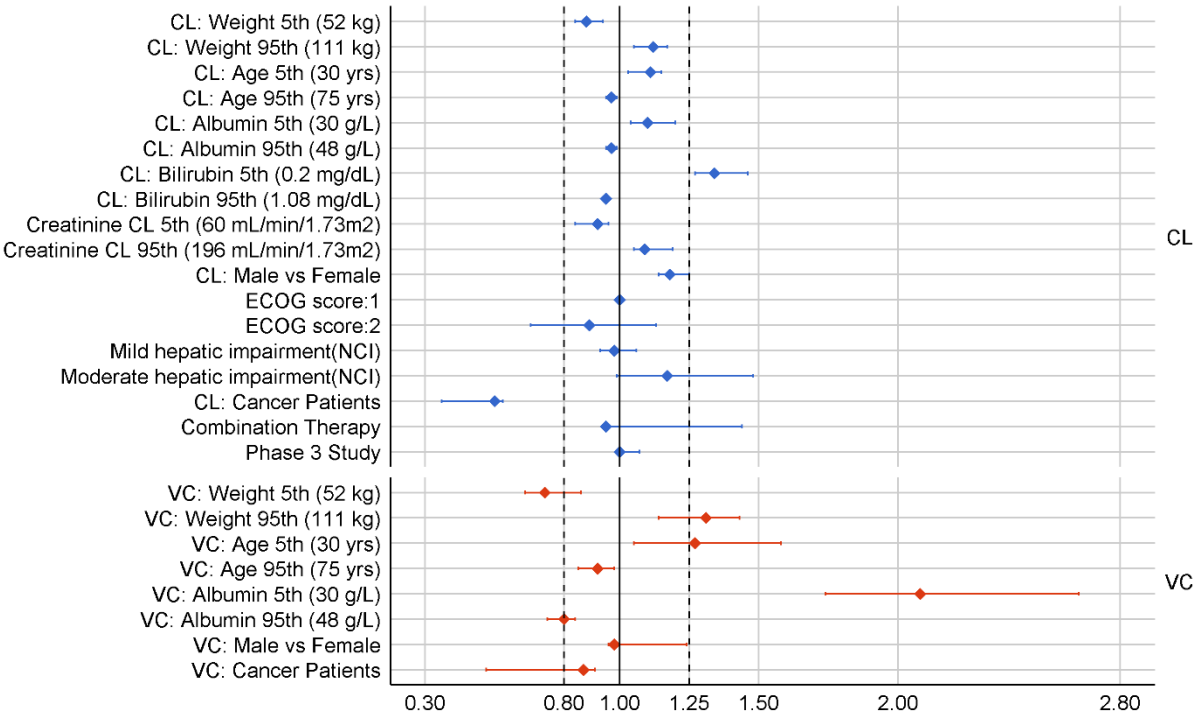
Table 80: Final Population PK Parameters of Full model of Binimetinib.

Parameter	Estimate	Bootstrap Median	CV	95% CI
CL	19	19	4.99	(17.4, 20.2)
VC	14.9	14.9	39.01	(13.1, 20.8)

Q	7.8	7.8	4.6	(7.11, 8.26)
VP	185	185	9.18	(160, 216)
KA	0.423	0.422	4.76	(0.383, 0.443)
Lag Time	0.217	0.223	4.99	(0.208, 0.248)
Additive Error	-0.481	-0.467	-4.54	(-0.502, -0.439)
Emax	-0.842 FIX			
T50	81.3 FIX			
CL_Age	-0.176	-0.149	-41.58	(-0.21, -0.042)
CL_WT	0.36	0.314	28.45	(0.148, 0.434)
CL_Albumin	-0.266	-0.277	-35.38	(-0.505, -0.119)
CL_Bilirubin	-0.196	-0.203	-12.9	(-0.261, -0.162)
CL_Combo	-0.06	-0.056	824.78	(-0.067, 0.361)
CL_Creatinine CL	0.138	0.146	36.59	(0.076, 0.297)
CL_Disease State	-0.576	-0.595	-48.91	(-1.02, -0.547)
CL_ECOG 1	0.0001	0	6257.97	(-0.002, 0.003)
CL_ECOG 2	-0.0695	-0.118	-143.34	(-0.387, 0.125)
CL_Mild Hepatic Impairment	-0.0165	-0.016	-338.35	(-0.074, 0.056)
CL_Moderate Hepatic Impairment	0.138	0.156	70.12	(-0.005, 0.394)
CL_Phase 3	-0.00162	0.005	151.1	(-0.004, 0.066)
CL_Sex	0.171	0.168	17.03	(0.129, 0.223)
V_Age	-0.358	-0.358	-46.8	(-0.674, -0.069)
V_Albumin	-1.97	-2.03	-17.36	(-2.71, -1.54)
V_Disease State	-0.109	-0.134	-118.23	(-0.65, -0.092)
V_Sex	-0.0213	-0.017	595.5	(-0.037, 0.214)
V_WT	0.809	0.768	30.69	(0.367, 1.02)
ω^2- CL [-]	0.056	0.054	12.81	(0.041, 0.056)
ω^2- Q [-]	0.139	0.139	20.18	(0.102, 0.191)
ω^2- VP [-]	0.645	0.642	15.67	(0.384, 0.773)
ω^2- Ka [-]	0.199	0.197	22.52	(0.123, 0.225)
ω^2- VC [-]	0.31	0.312	34.07	(0.283, 0.628)
ω^2- Alag [-]	0.288	0.282	12.06	(0.207, 0.304)
ω^2- Emax [-]	0.029	0.029	111.49	(0.024, 0.046)

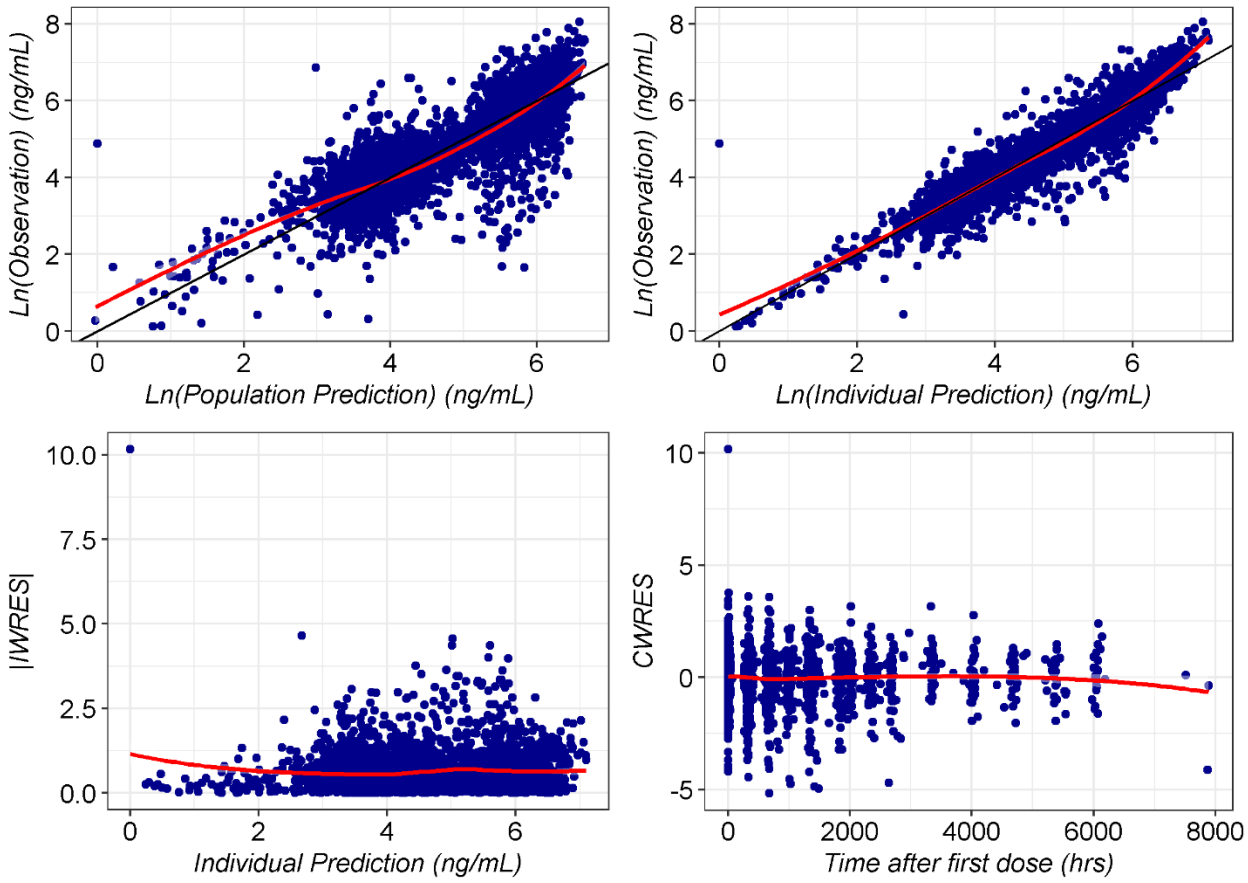
Source: Reviewer's analysis based on popPK dataset "allpkdat.xpt"

Figure 17: Covariate Effects on Binimetinib PK Parameters



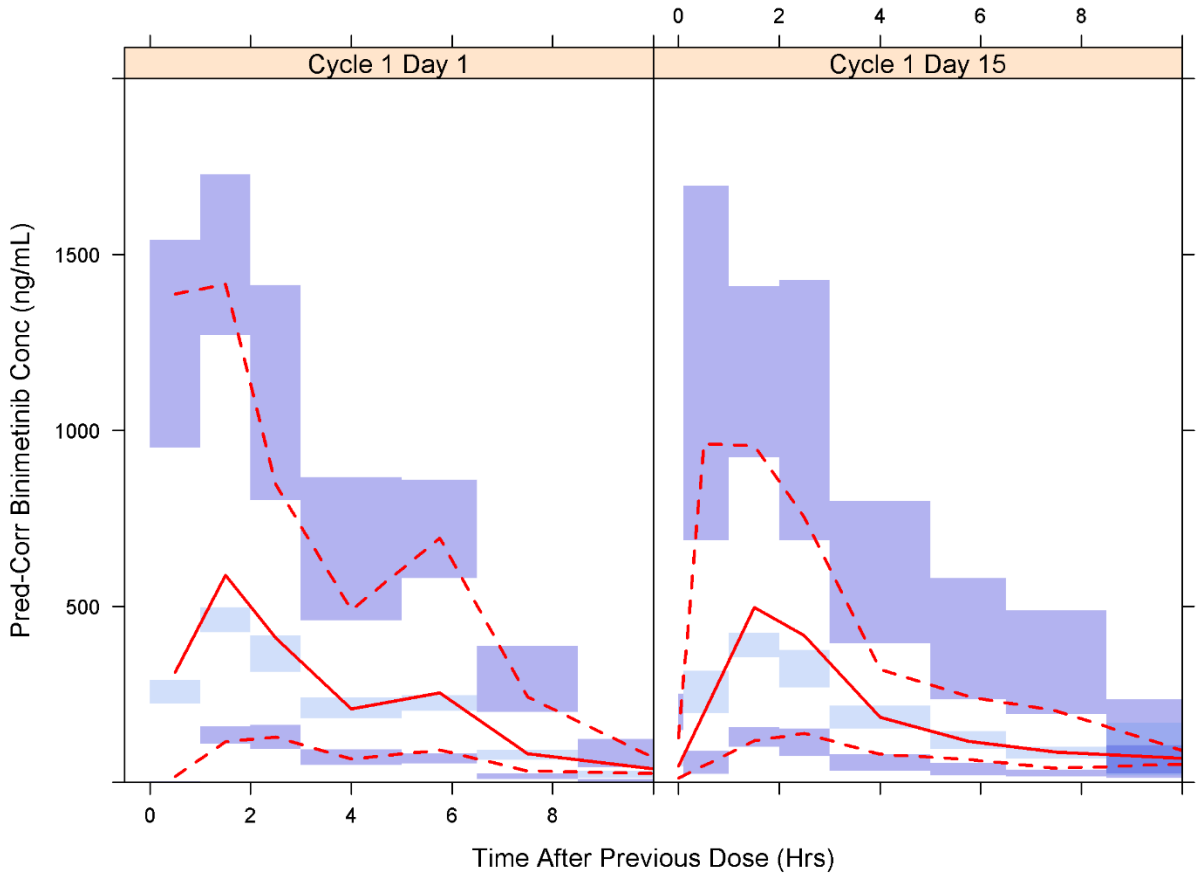
Source: Reviewer's analysis based on popPK dataset "allpkdat.xpt"

Figure 18: Goodness-of-fit Plots of Binimetinib in All Patients in Study ARRAY-162-105, CMEK162X2110, CLGX818X2109 and CMEK162B2301 Part 1.



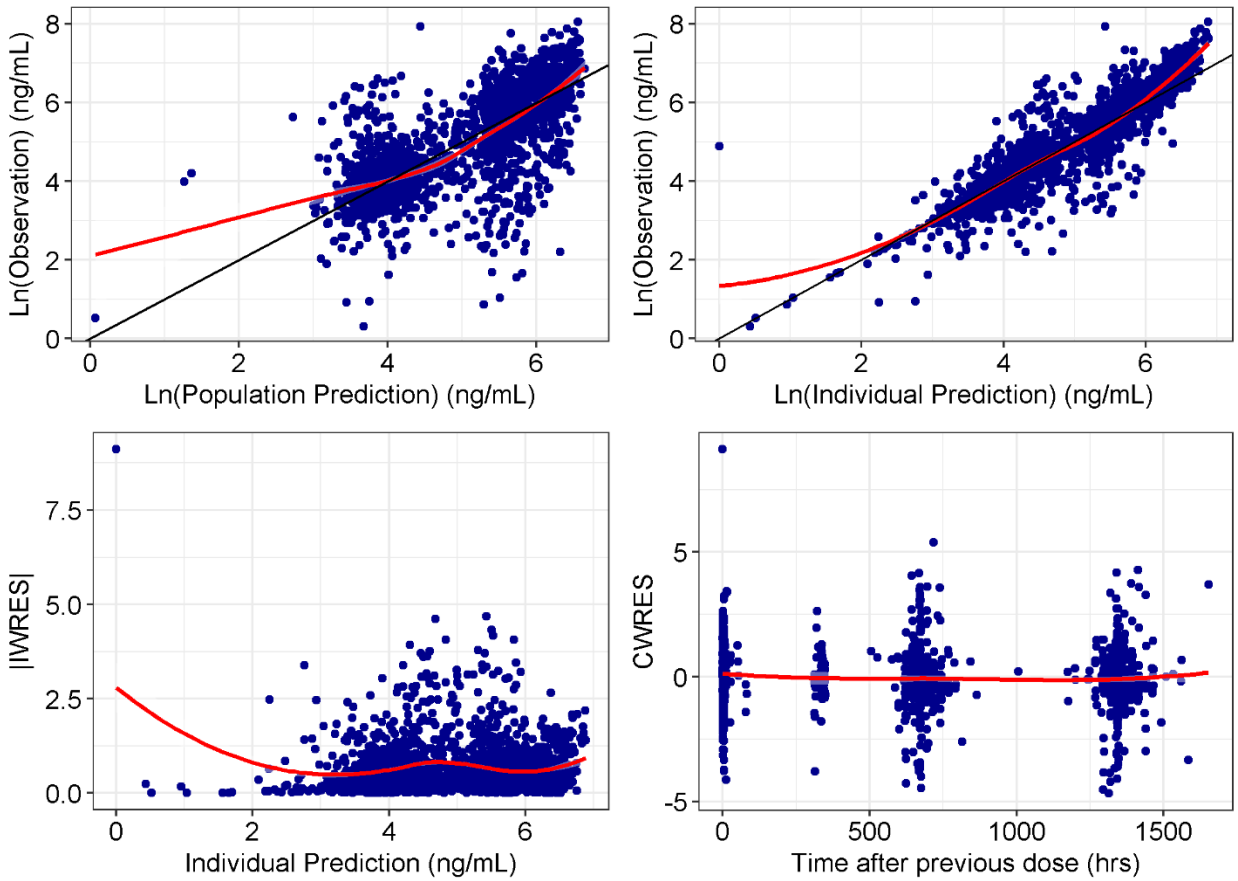
Source: Reviewer's analysis based on popPK dataset "allpkdat.xpt"

Figure 19: Prediction-corrected Visual Predictive Check for Binimetinib PK profile at Cycle 1 Day 1 and Cycle 1 Day 15.



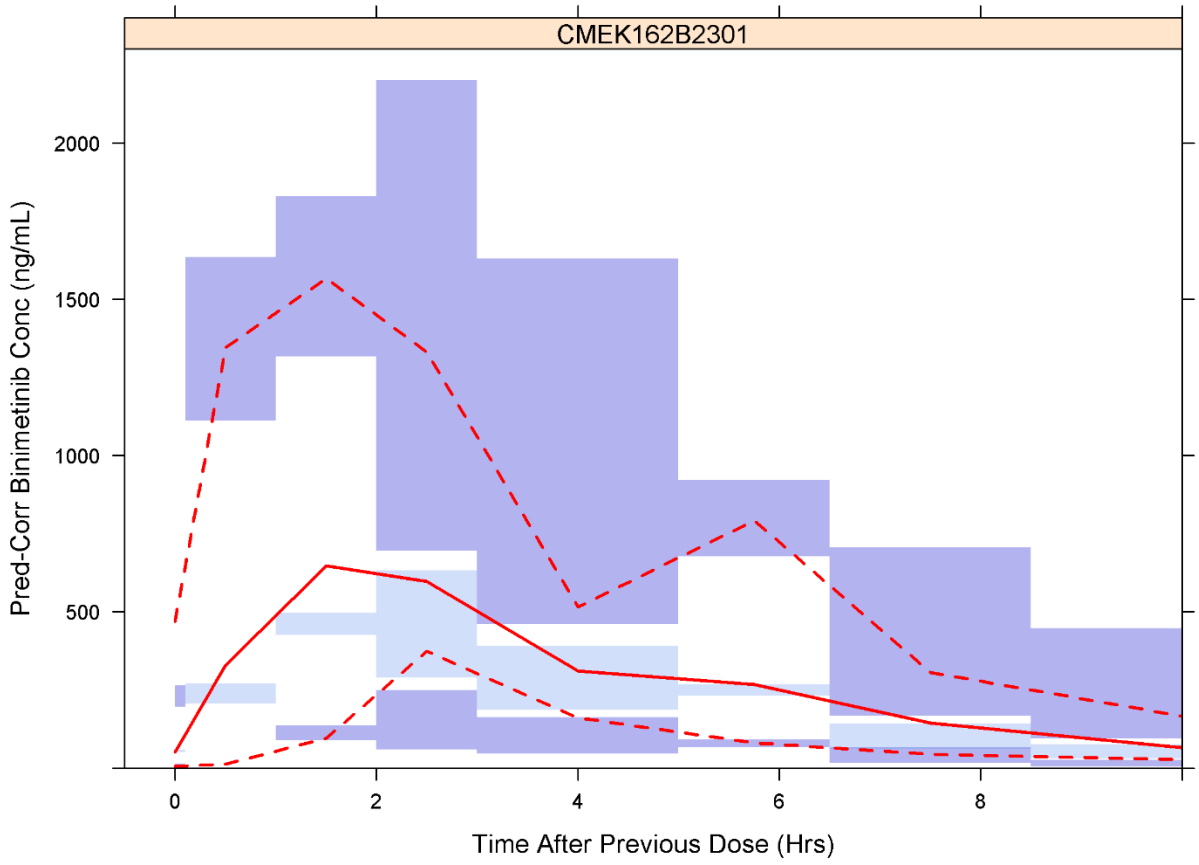
Source: Reviewer's analysis based on popPK dataset "allpkdat.xpt"

Figure 20: Goodness-of-fit Plots of Binimetinib in Patients from Part 1 and Part 2 in Study CMEK162B2301



Source: Reviewer's analysis based on popPK dataset "allpkdat.xpt"

Figure 21: Prediction-corrected Visual Predictive Check for Binimetinib PK profile in Study CMEK162B2301



Source: Reviewer's analysis based on popPK dataset "allpkdat.xpt"

Table 81: Summary of Exposure Metrics of Binimetinib Administered in Combination with Encorafenib in COLUMBUS study.

ARM	PARA	Geom_Mean	CV	Min	Max
Combo MEK162 at 45 mg LGX818 at 300 mg	AUCinf	2490.764	31.52	937.47	6326.11
Combo MEK162 at 45 mg LGX818 at 450 mg	AUCinf	2573.254	35.49	1118.46	9217.85
Combo MEK162 at 45 mg LGX818 at 300 mg	Cmax	466.13	25.56	156.87	865.67
Combo MEK162 at 45 mg LGX818 at 450 mg	Cmax	486.911	26.93	148.35	1179.92
Combo MEK162 at 45 mg LGX818 at 300 mg	Half.life	4.822	26.39	2.23	12.78
Combo MEK162 at 45 mg LGX818 at 450 mg	Half.life	4.715	23.87	2.58	10.08
Combo MEK162 at 45 mg LGX818 at 300 mg	Cmin	51.614	45.01	10.063	167.018
Combo MEK162 at 45 mg LGX818 at 450 mg	Cmin	53.323	49.18	13.469	233.457

Source: Reviewer's analysis based on popPK dataset "allpkdat.xpt"

19.2.2. **Dose-Response Analyses**

Study CMEK162B2301 is an ongoing 2-part, multicenter, randomized, open label, Phase 3 study comparing the efficacy and safety of encorafenib plus binimetinib to vemurafenib and encorafenib monotherapy in patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation. Part 1 of the study was designed to evaluate the activity of encorafenib 450 mg QD plus binimetinib 45 mg BID (Combo 450) vs. vemurafenib. Part 2 was designed to further define and characterize the contribution of binimetinib to the combination using the same encorafenib dose, 300 mg QD, in the combination (Combo 300) and the single-agent encorafenib arm (Mono 300). The summary of baseline covariates in Combo 450 and Mono 300 in Part 1 and Combo 300 and Mono 300 in Part 2 were provided in Table 82. The distribution of age and ECOG status were similar across treatment groups in Part 1 and 2. However, the median LDH value in monotherapy Part 2 appears to be higher than the Combo 450 in Part 2 and both monotherapy and combination treatment groups in Part 1. A higher percentage of patients (~10%) in monotherapy Part 2 have stage IV M1C with elevated LDH compared to other treatment groups.

One of the key clinical pharmacology review question is whether the encorafenib 450mg QD in combination with binimetinib 45mg BID can provide better benefit-risk profile than encorafenib 300mg QD in combination with the same dose of binimetinib. The independent dose/exposure-response analyses were conducted to help address this question. As Combo 450 arm and Combo 300 arm were not randomized groups and evaluated in different time, we will use encorafenib monotherapy which were tested in both parts as comparator in comparing these two doses. A direct comparison between these two doses were also conducted after controlling for the baseline covariates.

Table 82: Baseline Characteristics in Part 1 and Part 2 of Study CMEK162B2301.

Baseline Characteristics	Monotherapy (Part 1) (n=191)	Monotherapy (Part 2) (n=84)	Combo 450 (Part 1) (n=192)	Combo 300 (Part 2) (n=257)	Overall (n=724)
Age (years)					
Mean (CV%)	54.5 (23.2%)	56.2 (26.0%)	56.2 (24.2%)	57.4 (24.4%)	56.2 (24.3%)
Median [Min, Max]	54.0 [23.0, 88.0]	57.5 [19.0, 81.0]	57.0 [20.0, 89.0]	58.0 [20.0, 94.0]	56.5 [19.0, 94.0]
LDH (U/L)					
Mean (CV%)	267 (94.7%)	342 (109%)	299 (124%)	301 (106%)	296 (110%)
Median [Min, Max]	189 [75.0, 1890]	221 [115, 2100]	173 [76.0, 3590]	201 [103, 3100]	192 [75.0, 3590]
≤270 U/L (ULN)	151 (79.1%)	55 (65.5%)	142 (74.0%)	185 (72.0%)	533 (73.6%)
>270 U/L (ULN)	40 (20.9%)	29 (34.5%)	80 (26.0%)	72 (28.0%)	191 (26.4%)
Sex					
Female	86 (45.0%)	42 (50.0%)	77 (40.1%)	107 (41.6%)	312 (43.1%)
Male	105 (55.0%)	42 (50.0%)	115 (59.9%)	150 (58.4%)	412 (56.9%)
Race					
White	171 (89.5%)	77 (91.7%)	181 (94.3%)	236 (91.8%)	665 (91.9%)
Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.1%)
Asian	6 (3.1%)	7 (8.3%)	5 (2.6%)	15 (5.8%)	33 (4.6%)
Other	2 (1.0%)	0 (0.0%)	3 (1.6%)	2 (0.8%)	7 (1.0%)
Unknown	9 (4.7%)	0 (0.0%)	2 (1.0%)	3 (1.2%)	14 (1.9%)
American Indian or Alaska Native	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Missing	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	2 (0.3%)
ECOG n (%)					
ECOG=0	138 (72.3%)	60 (71.4%)	136 (70.8%)	189 (73.5%)	523 (72.2%)
ECOG=1	53 (27.7%)	24 (28.6%)	56 (29.2%)	68 (26.5%)	201 (27.8%)
Cancer Stage					
Stage IIIB	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Stage IIIC	4 (2.1%)	5 (6.0%)	9 (4.7%)	8 (3.1%)	26 (3.6%)
Stage IV M1A	29 (15.2%)	12 (14.3%)	26 (13.5%)	31 (12.1%)	98 (13.5%)
Stage IV M1B	38 (19.9%)	10 (11.9%)	34 (17.7%)	47 (18.3%)	129 (17.8%)
Stage IV M1C with elevated LDH	50 (26.2%)	32 (38.1%)	50 (26.0%)	72 (28.0%)	204 (28.2%)
Stage IV M1C with normal LDH	68 (35.6%)	25 (29.8%)	73 (38.0%)	99 (38.5%)	265 (36.6%)

CV= Coefficient of variation; ECOG= Eastern Cooperative Oncology Group; Max= Maximum; Min= Minimum; n= Number of subjects; ULN= Upper limit of normal
Note: A total of 6 subjects did not have concentrations of binimetinib or encorafenib. Only subjects included in the PK analysis were retained for the descriptive statistics.

Source: Applicant's Pop-PK report amendment, Table 2, Page 17

19.2.2.1 Dose-Response Analyses for Efficacy

Multiple efficacy endpoints including ORR, PFS and OS were compared between Combo 300 and Combo 450. The results of confirmed ORR by BIRC were first compared. The confirmed ORR appears to be comparable between Combo 450 (63.0 (95% CI: 55.8, 69.9)) and Combo 300 (65.9 (95% CI: 59.8, 71.7)), and ORR in 2 monotherapy arms in Part 1 (50.5%) and Part 2 (50.4%) are also comparable.

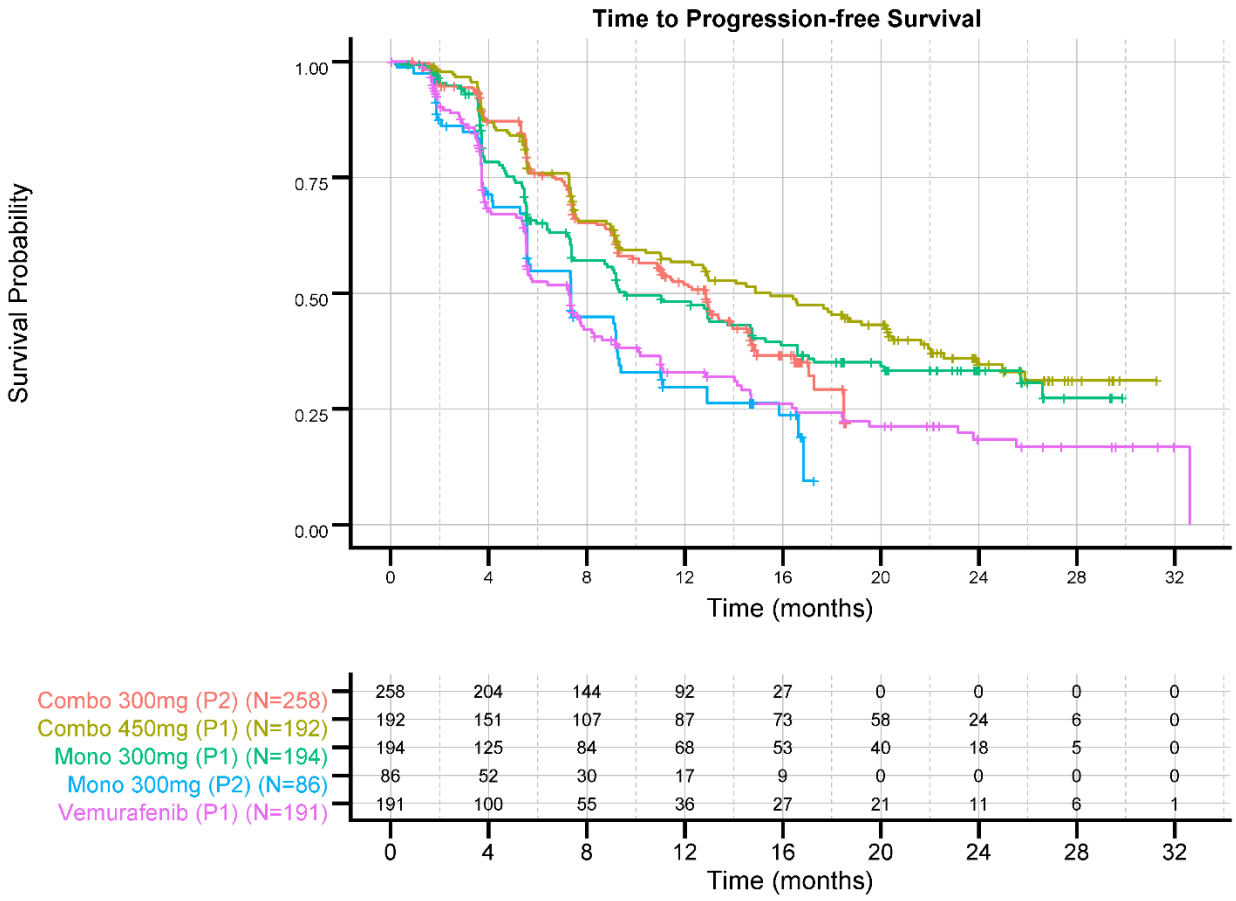
The Kaplan-Meier (KM) curve of PFS for monotherapy and combination therapy in each part of study CMEK162B2301 were presented in Figure 22. The median time to PFS is 15.5 months for Combo 450 and 9.56 months for Mono 300 in part 1, and 12.88 months for Combo 300 and 7.36 months for Mono 300 in part 2, respectively. The numerical increase in median PFS

comparing combination therapy to its randomized monotherapy is comparable (5.94 months vs 5.52 months). The difference in time to PFS between different treatment groups were characterized by a Cox proportional-hazards (CPH) model. A full model approach was first applied to incorporate all the known risk factors. The covariates with p-value larger than 0.05 were removed from the full model after backward elimination. The risk factors included in the full model include: Age, Gender, Body weight, Race, Region, Primary tumor site, Metastatic disease, Cancer stage at baseline per IWRS, Brain Metastases, Baseline LDH, ECOG score, BRAF mutation status and Number of organs.

The HRs obtained from final Cox regression characterizing direct comparison of time to PFS of Combo 450 versus Mono 300 in Part 1, Combo 300 versus Mono 300 in Part 2 and cross-part comparison of Combo 450 versus Combo 300 and Mono 300 in Part 1 versus Part 2 were provided in Table 83. Both combination doses showed a (nominally) statistically significant improvement in PFS compared to its randomized monotherapy after adjusting for baseline covariates. The HR comparing Combo 300 to Mono 300 in part 2, 0.56 (95% CI: 0.41, 0.77), is numerically lower than the HR comparing Combo 450 to Mono 300 in part 1, 0.75 (95% CI: 0.56, 0.99).

Time to PFS was also compared between two encorafenib monotherapies in Part 1 and Part 2 to evaluate whether efficacy results between Part 1 and Part 2 are comparable. Based on cox regression after adjusting for significant baseline covariates, patients receiving Mono 300 in Part 2 had a trend of higher risk of progression or death compared to patients receiving Mono 300 in Part 1 (HR: 1.29, 95% CI: 0.92, 1.82).

Figure 22: The Kaplan-Meier (KM) Curve of PFS for Monotherapy and Combination Therapy in Part 1 and Part 2 of Study CMEK162B2301.



Source: Reviewer's analysis based on dataset "adtte.xpt"

Table 83: HRs of Dose Comparison and Significant Baseline Covariates of Final D-R Model of PFS.

Covariate	HR	Lower 95% CI	Upper 95% CI	P-value
Combo 450 vs Mono 300(P1)	0.747	0.564	0.99	0.0427
STAGE IV M1A	1.93	0.444	8.34	0.381
STAGE IV M1B	4.33	1.04	18	0.0435
STAGE IV M1C WITH ELEVATED LDH	3.07	0.721	13.1	0.129
STAGE IV M1C WITH NORMAL LDH	3.37	0.825	13.8	0.0906
ECOG Score:1	1.48	1.09	2.02	0.0132
Male vs Female	1.37	1.03	1.83	0.0305
Log(Baseline LDH)	2.93	2.1	4.09	2.85E-10
Combo 300 vs Mono 300(P2)	0.559	0.407	0.769	0.000355
ECOG Score:1	1.53	1.11	2.12	0.0102
Number of Organs>3	1.65	1.08	2.5	0.0196

Number of Organs=2	0.882	0.572	1.36	0.571
Number of Organs=3	1.22	0.794	1.88	0.363
Male vs Female	1.43	1.06	1.94	0.0204
Log(Baseline LDH)	2.26	1.76	2.89	1.59E-10
Combo 450 vs Combo 300	0.836	0.634	1.1	0.202
ECOG Score:1	1.46	1.1	1.94	0.00864
Male vs Female	1.45	1.11	1.9	0.00607
Log(Baseline LDH)	2.75	2.25	3.37	0
Mono 300(P2) vs Mono 300(P1)	1.29	0.918	1.82	0.142
STAGE IV M1A	0.0517	0.00717	0.374	0.00332
STAGE IV M1B	0.116	0.0168	0.804	0.0292
STAGE IV M1C WITH ELEVATED LDH	0.112	0.0163	0.776	0.0266
STAGE IV M1C WITH NORMAL LDH	0.134	0.0197	0.916	0.0404
ECOG Score:1	1.72	1.22	2.42	0.00203
Metastatic Disease	28.1	2.02	392	0.013
Log(Baseline LDH)	2.41	1.7	3.42	7.00E-07

Source: Reviewer's analysis based on dataset "adtte.xpt"

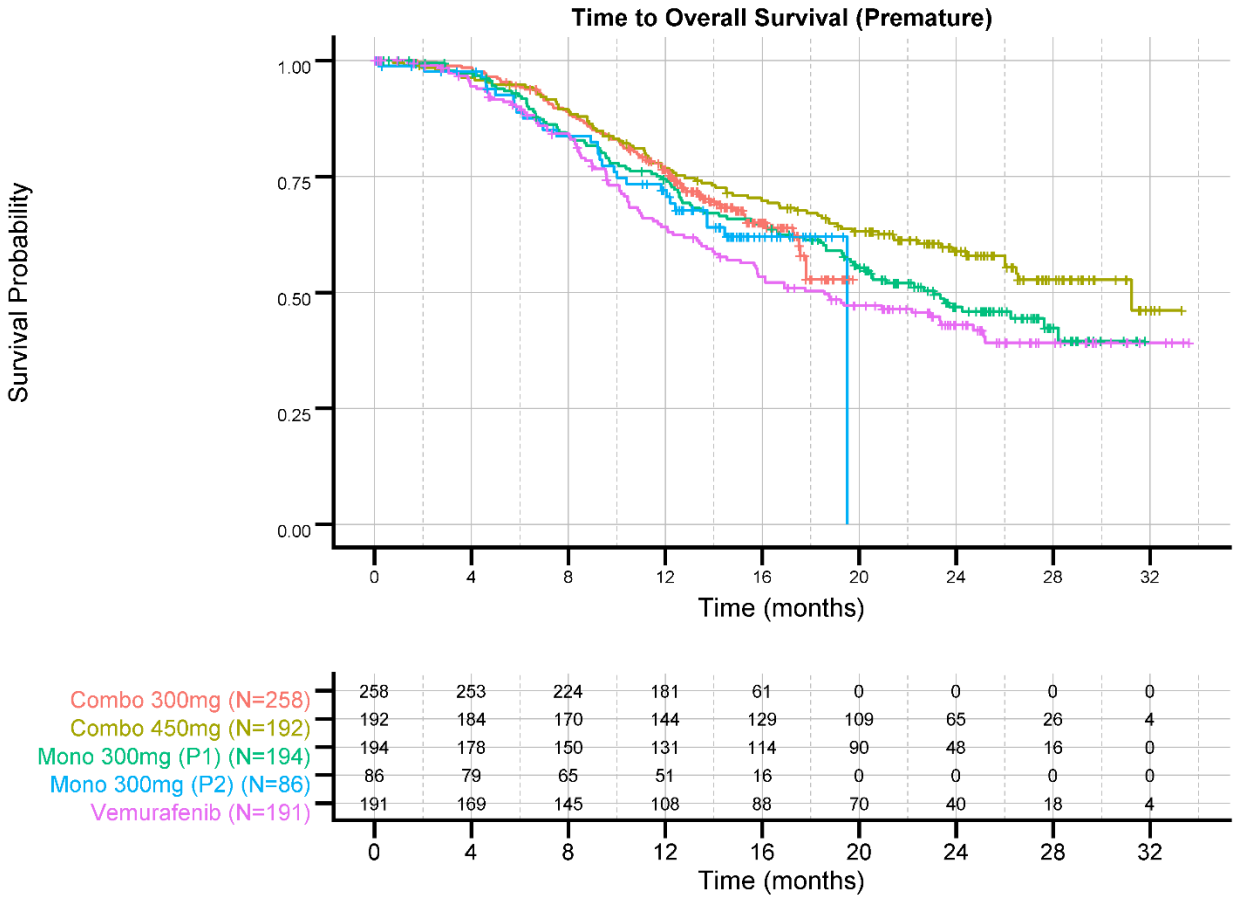
The overall survival (OS) data is still premature to conduct formal analysis. Per study protocol, the interim analysis will be conducted when approximately 232 OS events have occurred in the Combo 450 and vemurafenib arms combined. An independent OS analysis was conducted by the reviewer based on the data pertaining to dates of deaths and survival follow-up status as of 09 November 2016. There is a total of 81 events out of 192 patients treated with Combo 450, 86 events out of 258 patients treated with Combo 300 and 98 events out of 191 patients treated with vemurafenib based on the data in applicant's original submission. In addition, there are 94 events out of 194 patients and 29 events out of 86 patients in the Mono 300 in Part 1 and 2, respectively.

The Kaplan-Meier (KM) curve of OS for monotherapy and combination therapy in each part of study CMEK162B2301 were presented in Figure 23. The median time to OS is 31.2 months for Combo 450, and 23.1 and 19.5 months for Mono 300 in Part 1 and Part 2, respectively. The median OS is not reached for Combo 300 based on available data. The median follow-up is 10 months shorter in Combo 300 (15 months) compared to Combo 450 (25 months) The difference in time to OS between different treatment groups were characterized by a Cox proportional-hazards (CPH) model. Stepwise selection was conducted to screen significant covariates to be included in the final model. The model selection and the covariates included in the full model were same as those in the cox analysis for PFS. The HRs obtained from final cox regression characterizing randomized comparison of Combo 450 versus Mono 300 in Part 1, Combo 300 versus Mono 300 in Part 2 and cross-part comparison of Combo 450 versus Combo 300 and Mono 300 Part 1 versus Part 2 were provided in Table 84.

The patients treated with Combo 450 had a (nominally) statistically significantly lower risk of death compared to its randomized monotherapy after adjusting for baseline covariates, and the

HR comparing Combo 450 to Mono 300 in Part 1 is numerically lower than the HR comparing Combo 300 to Mono 300 in part 2 (0.658 (95% CI: 0.486, 0.892) vs. 0.824 (0.537, 1.26)). The cross-part comparison between two combination therapies showed that patients treated with Combo 450 had a trend of lower risk of death compared to Combo 300 with HR estimated to be 0.729 (95% CI: 0.519, 1.02). In addition, no strong difference in risks of death were found between patients receiving Mono 300 in Part 1 and Part 2 (HR: 0.973, 95% CI: 0.616, 1.54, although the median OS in part 2 is 3.6 months shorter). The results from dose response analyses for OS are preliminary and should be interpreted with caution as it is important to note that both arms are immature, especially considering patients treated in Part 2 are followed approximately 10 months shorter than the patients in Part 1.

Figure 23: The Kaplan-Meier (KM) Curve of Preliminary OS for Monotherapy and Combination Therapy in Part 1 and Part 2 of Study CMEK162B2301.



Source: Reviewer's analysis based on dataset "adsl.xpt"

Table 84: HRs of Dose Comparison and Significant Baseline Covariates of Final D-R Model of OS.

Covariate	HR	Lower 95% CI	Upper 95% CI	P-value
Combo 450 vs Mono 300(P1)	0.658	0.486	0.892	0.00702
Male vs Female	1.46	1.07	2	0.0165
STAGE IV M1A	0.378	0.199	0.72	0.00307
STAGE IV M1B	1.09	0.713	1.67	0.688
STAGE IV M1C WITH ELEVATED LDH	0.78	0.466	1.31	0.344
Log(Baseline LDH)	3.56	2.49	5.09	3.74E-12
Combo 300 vs Mono 300(P2)	0.824	0.537	1.26	0.376
ECOG Score:1	2.39	1.63	3.51	9.28E-06
Non-Caucasian vs Caucasian	0.216	0.0676	0.689	0.00963
STAGE IIIC	0.168	0.0229	1.23	0.0793
STAGE IV M1A	0.441	0.186	1.04	0.0623
STAGE IV M1B	0.605	0.316	1.16	0.128
STAGE IV M1C WITH ELEVATED LDH	0.695	0.415	1.16	0.167
Log(Baseline LDH)	2.88	2.07	4.01	4.02E-10
Combo 450 vs Combo 300	0.729	0.519	1.02	0.0675
ECOG Score:1	1.69	1.22	2.34	0.00147
Number of Organs>3	1.64	1.03	2.63	0.038
Number of Organs=2	0.948	0.584	1.54	0.828
Number of Organs=3	1.35	0.842	2.15	0.215
Primary Site: Unknown	0.364	0.115	1.15	0.0859
Log(Baseline LDH)	2.74	2.18	3.44	0
Mono 300(P2) vs Mono 300(P1)	0.973	0.616	1.54	0.906
Age	0.983	0.968	0.998	0.0299
ECOG Score:1	1.71	1.16	2.52	0.00641
Male vs Female	1.5	1.03	2.18	0.0365
STAGE IV M1A	0.193	0.0762	0.489	0.00053
STAGE IV M1B	0.924	0.538	1.59	0.775
STAGE IV M1C WITH ELEVATED LDH	0.784	0.441	1.39	0.406
Log(Baseline LDH)	3.06	2.02	4.65	1.51E-07

Source: Reviewer's analysis based on dataset "adsl.xpt"

19.2.2.2 Dose-Response Analyses for Safety

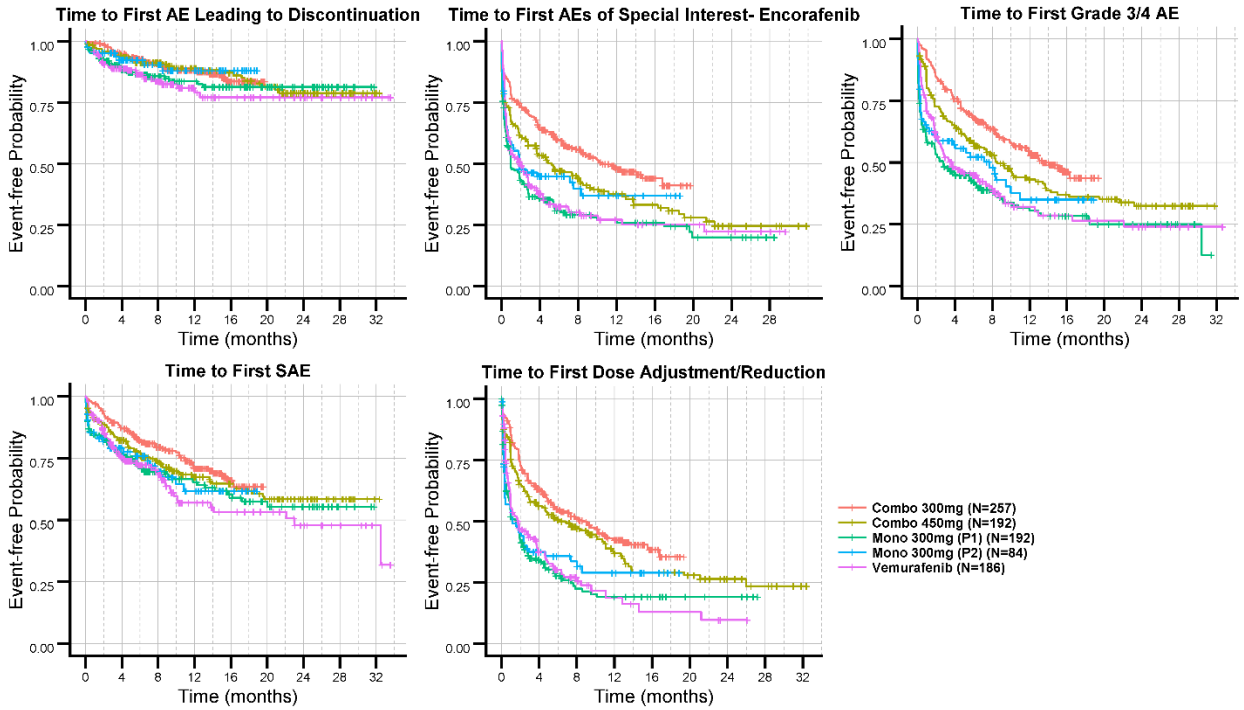
The safety profile between Combo 450 and Combo 300 were also compared. Time to general safety event or time to safety event of special interest were compared between two combo doses using Cox proportional analysis. The HR of time to evaluated safety event of combination therapy (Combo 450 or Combo 300) relative to its randomized monotherapy in each part was

estimated and compared. A cross-part comparison between two combo doses was also conducted using cox proportional hazard model.

For general safety profiles, time to occurrence of first AE leading to drug discontinuation, first safety event of special interest of encorafenib, first dose adjustment/reduction, first grade 3/4 AE and first SAE were compared between treatment groups in study CMEK162B2301. The Kaplan-Meier (KM) curve of time to general safety events of interest in each part of study CMEK162B2301 were presented in Figure 24. The combination therapy appears to have a better safety profile than monotherapy and vemurafenib arm. In general median time to safety event also appears to be longer in Combo 300 than Combo 450.

The HRs obtained from final Cox regression comparing time to general safety events of interest of Combo 450 to Mono 300 in Part 1, Combo 300 to Mono 300 in Part 2 and Combo 450 to Combo 300 were provided in Table 85. It was also visualized in the forest plot shown in Figure 25. The HR comparing Combo 300 to Mono 300 in Part 2 is numerically lower than the HR comparing Combo 450 to Mono 300 in Part 1 for time to first safety event of special interest of encorafenib, first dose adjustment/reduction, first grade 3/4 AE and first SAE. Cross-part comparison shows patients in Combo 450 had a (nominally) statistically significantly higher risk of having special interest of encorafenib and grade 3/4 AE compared to Combo 300 with HR estimated to be 1.47 (95% CI: 1.14, 1.91) and 1.46 (95% CI: 1.12, 1.9), respectively. Patients in Combo 450 also tend to have higher risks of experiencing SAE and dose adjustment/reduction compared to Combo 300, but the difference is not statistically significant. For the time to first AE leading to discontinuation, there appears to be no difference between Combo 450 and Combo 300.

Figure 24: The Kaplan-Meier (KM) Curve of Time to Evaluated General Safety Event in Part 1 and Part 2 of Study CMEK162B2301.



Source: Reviewer's analysis based on dataset "adttes.xpt"

Table 85: Parameter Estimates of Final D-R Model of General Safety Events Comparing Combo 450 to Mono (P1), Combo 400 to Mono (P2) and Combo 450 to Combo 300.

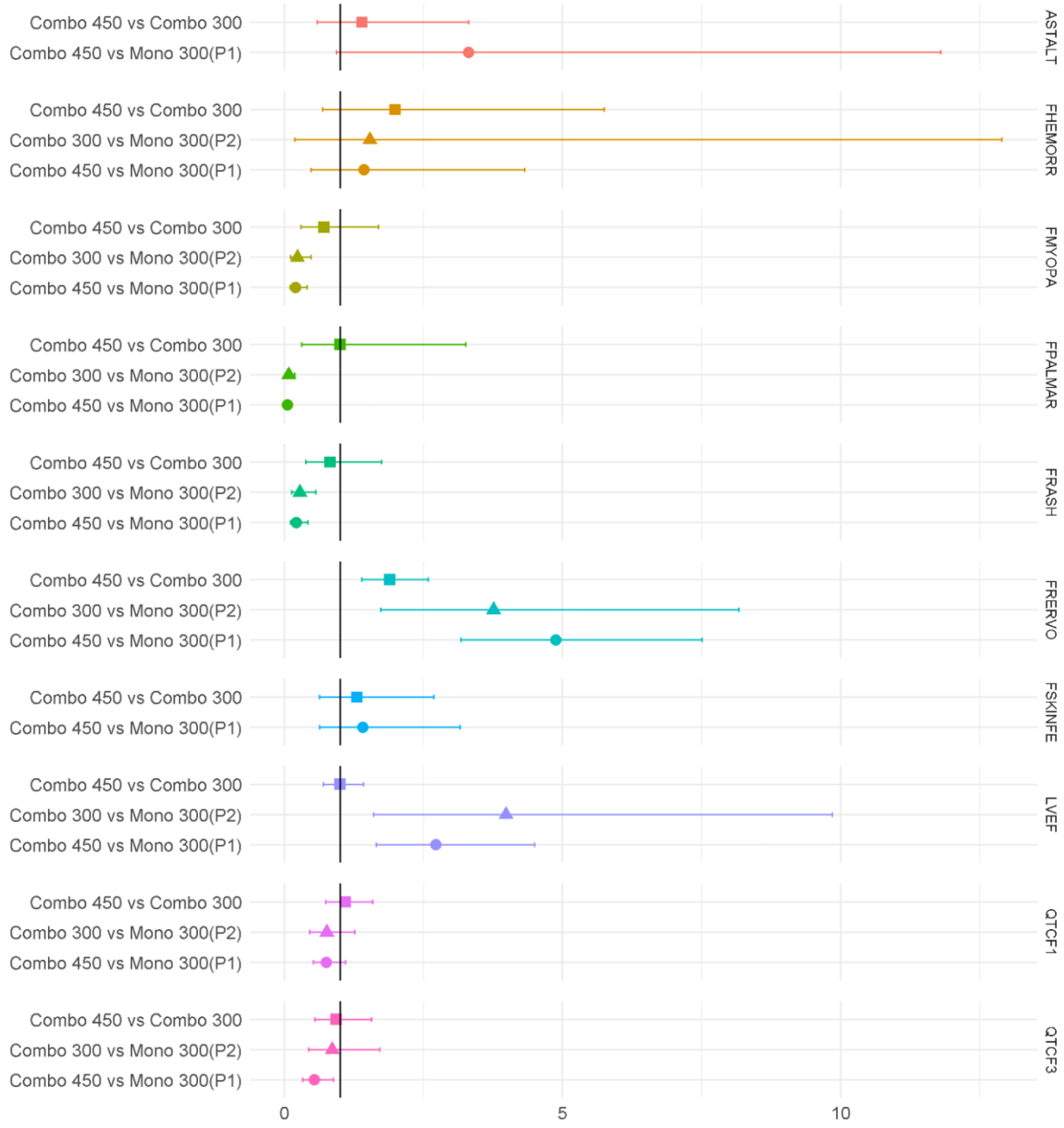
Covariate	HR	Lower 95% CI	Upper 95% CI	P-value
Time to first AE requiring dose discontinuation				
Age	1.03	1.01	1.06	0.00162
Europe	0.217	0.0651	0.726	0.0131
North America	0.727	0.202	2.62	0.626
Other	0.163	0.027	0.983	0.0478
Male vs Female	0.575	0.336	0.985	0.0439
Combo 450 vs Mono 300(P1)	0.822	0.485	1.39	0.465
ECOG Score:1	2.07	1.08	3.95	0.0282
Combo 300 vs Mono 300(P2)	0.986	0.452	2.15	0.973
Age	1.03	1.01	1.05	0.00436
Combo 450 vs Combo 300	0.993	0.579	1.7	0.978
Time to first AE of special interest of encorafenib				
ECOG Score:1	0.666	0.498	0.89	0.00605
Europe	0.737	0.346	1.57	0.428
North America	1.96	0.87	4.43	0.104
Other	0.691	0.284	1.68	0.414
Combo 450 vs Mono 300(P1)	0.76	0.592	0.975	0.031

Combo 300 vs Mono 300(P2)	0.614	0.439	0.858	0.00429
ECOG Score:1	0.632	0.462	0.863	0.00396
Europe	0.531	0.195	1.44	0.214
North America	1.14	0.391	3.35	0.806
Other	0.501	0.171	1.47	0.208
Combo 450 vs Combo 300	1.47	1.14	1.91	0.00331
Time to first Grade 3/4 AE				
Age	1.02	1.01	1.03	0.00013
Combo 450 vs Mono 300(P1)	0.589	0.455	0.763	6.17E-05
Combo 300 vs Mono 300(P2)	0.551	0.39	0.779	0.000737
Log(Baseline LDH)	1.41	1.1	1.81	0.00732
Age	1.01	1	1.02	0.00384
Combo 450 vs Combo 300	1.46	1.12	1.9	0.00456
Log(Baseline LDH)	1.33	1.08	1.63	0.00754
Time to first serious AE				
Age	1.02	1.01	1.03	0.00745
Male vs Female	1.5	1.04	2.15	0.0285
Combo 450 vs Mono 300(P1)	0.764	0.538	1.08	0.131
Log(Baseline LDH)	1.92	1.49	2.49	6.47E-07
Age	1.02	1	1.03	0.0376
Combo 300 vs Mono 300(P2)	0.69	0.436	1.09	0.112
Log(Baseline LDH)	1.89	1.4	2.55	3.64E-05
Age	1.02	1.01	1.03	0.00445
Combo 450 vs Combo 300	1.31	0.927	1.85	0.126
Log(Baseline LDH)	1.88	1.47	2.4	3.71E-07
Time to first dose adjustment/reduction				
Age	1.01	1	1.02	0.0172
BRAF:V600E	0.621	0.421	0.914	0.0157
Non-Caucasian	1.67	1.03	2.7	0.037
Europe	0.402	0.176	0.919	0.0308
North America	0.626	0.258	1.52	0.3
Other	0.425	0.163	1.11	0.0805
STAGE IIIC	1.43	0.779	2.61	0.25
STAGE IV M1A	1.46	1.01	2.11	0.0428
STAGE IV M1B	1.01	0.71	1.43	0.957
STAGE IV M1C WITH ELEVATED LDH	0.687	0.486	0.971	0.0334
Combo 450 vs Mono 300(P1)	0.531	0.41	0.687	1.45E-06
Combo 300 vs Mono 300(P2)	0.517	0.376	0.709	4.44E-05
BRAF: V600E	0.603	0.431	0.845	0.00325
Combo 450 vs Combo 300	1.27	0.99	1.63	0.0595

Source: Reviewer's analysis based on dataset "adttes.xpt"

Time to event analysis were also conducted using Cox regression analysis with same methodology for safety events of special interest which include: AST > 5x ULN or ALT > 5x ULN, Grade 2 or above Hemorrhage, Grade 2 or above Myopathy, Grade 2 or above Hand-Foot Syndrome, Grade 2 or above Rash, Grade 1 or above Retinopathy Excluding RVO, Grade 2 or above Skin Infections, definitive deterioration in LVEF, first QTcF increase from baseline>30 ms and first new QTcF>450 ms. The HRs obtained from final Cox regression comparing time to special safety events of interest of Combo 450 to Mono 300 in Part 1, Combo 300 to Mono 300 in Part 2 and Combo 450 to Combo 300 were visualized in Figure 25. Based on the Ccox regression analysis, patients in the combination therapy had (nominally) significantly lower risks of developing grade 2+ myopathy, grade 2+ hand-foot syndrome, grade 2+ rash compared to patients in the monotherapy. On the other hand, they have (nominally) significantly higher risks of experiencing definite deterioration in LVEF and grade 1+ retinopathy excluding RVO compared to patients in the monotherapy. No difference in time to occurrence was detected between Combo 450 and Combo 300 in the cross-part comparison except for grade 1+ retinopathy excluding RVO. Patients treated with Combo 450 had (nominally) significantly higher risks of developing grade 1+ retinopathy excluding RVO compared to patients in the Combo 300 group. The risks of developing liver toxicity or grade 2+ hemorrhage also appear to be higher in patients treated with combination therapy compared to monotherapy and in patients treated with Combo 450 compared to Combo 300, but the difference is not (nominally) statistically significant. For the time to first QTcF increase from baseline>30 ms and first new QTcF>450 ms, there appears to be no difference in it between Combo 450 and Combo 300.

Figure 25: The HRs Comparing Combination Therapy to the Randomized Monotherapy and HR Comparing Combo 450 to Combo 300 after Adjusting for Baseline Covariates for Evaluated Special Safety Event of Interest in Study CMEK162B2301.



**ASTALT: Time to AST > 5x ULN or ALT > 5x ULN; FHEMORR: Time to First Grade 2 or above Hemorrhage; FMYOPA: Time to First Grade 2 or above Myopathy; FPALMAR: Time to First Grade 2 or above Hand-Foot Syndrome; FRASH: Time to First Grade 2 or above Rash; FRERVO: Time to First Grade 1 or above Retinopathy Excluding RVO; FSKINFE: Time to First Grade 2 or above Skin Infections; LVEF: Time to Definitive Deterioration in LVEF; QTCF1: Time to First QTcF Increase from baseline>30 ms; QTCF3: Time to First new QTcF>450 ms*
Source: Reviewer's analysis based on dataset "adttes.xpt"

19.2.3. **Exposure Response Analyses**

The population of ER analysis between binimetinib exposure and efficacy and safety endpoints includes a total of 449 patients among whom 192 patients were treated with Combo 450 in Part 1 and 257 patients were treated with Combo 300 in Part 2. Model-predicted steady-state exposure metrics (SS Cavg, SS Ctrough and SS AUC) at day 15 were selected for the primary analyses of E-R. Pre-specified baseline covariates tested in dose-response analyses listed in section 19.4.2.1 were first added to the full models to adjust for potential confounding effects. The covariates with p-value larger than 0.05 were removed from the full model after backward elimination.

19.2.3.1 Binimetinib Exposure and Efficacy

The relationship between binimetinib exposure and objective response rate was characterized using logistic regression. The parameter estimates of the final logistic regression relating predicted steady state exposure metrics as continuous variable to ORR was provided in Table 86. The crude rates of objective response rates (ORRs) were also compared among patients in different exposure quartiles (Table 87). Overall, no associations were found between binimetinib exposure and ORR in 449 patients in study CMEK162B2301. Crude rates of ORR were found comparable between patients with low binimetinib exposure and patients with high binimetinib exposure.

Table 86: Parameter Estimates of Final Binimetinib E-R Model of ORR.

Covariate	Estimate	P-value	Lower 95% CI	Higher 95% CI
Intercept	5.036	0	2.441	7.748
Age	-0.018	0.02	-0.034	-0.003
AUCinf	0.059	0.627	-0.176	0.302
STAGE IIIC	-0.338	0.535	-1.38	0.791
STAGE IV M1A	-0.898	0.005	-1.525	-0.277
STAGE IV M1B	-0.041	0.891	-0.621	0.555
STAGE IV M1C WITH ELEVATED LDH	0.246	0.471	-0.415	0.926
Log(Baseline LDH)	-0.632	0.008	-1.113	-0.172
Intercept	5.052	0	2.493	7.726
Age	-0.019	0.015	-0.034	-0.004
CMIN	3.643	0.36	-4.006	11.679
STAGE IIIC	-0.361	0.507	-1.403	0.765
STAGE IV M1A	-0.906	0.004	-1.533	-0.284
STAGE IV M1B	-0.035	0.908	-0.615	0.562
STAGE IV M1C WITH ELEVATED LDH	0.247	0.468	-0.413	0.928
Log(Baseline LDH)	-0.639	0.007	-1.118	-0.179
Intercept	5.321	0	2.607	8.166
Age	-0.016	0.04	-0.032	-0.001
CMAX	-0.284	0.737	-1.95	1.383
STAGE IIIC	-0.28	0.608	-1.323	0.851

STAGE IV M1A	-0.894	0.005	-1.521	-0.274
STAGE IV M1B	-0.031	0.917	-0.613	0.566
STAGE IV M1C WITH ELEVATED LDH	0.261	0.446	-0.402	0.945
Log(Baseline LDH)	-0.653	0.007	-1.141	-0.186

Source: Reviewer's analysis based on dataset "adtte.xpt"

Table 87: Crude ORR Rates in Patients with Different Binimetinib Exposure Quartiles.

Exposure	Group	N	Responders (95% CI) (%)	HR (95% CI)	P-value
AUC	<Median	225	64.9 (58.2, 71.0)	0.9 (0.6, 1.36)	0.622
	>Median	224	64.7 (58.0, 70.9)		
Cmin	<Median	224	67 (60.3, 73.0)	1.23 (0.81, 1.86)	0.341
	>Median	225	62.7 (56.0, 68.9)		
Cmax	<Median	224	67.4 (60.8, 73.4)	1.12 (0.74, 1.69)	0.579
	>Median	225	62.2 (55.5, 68.5)		

Source: Reviewer's analysis based on dataset "adtte.xpt"

In addition, the relationship between binimetinib exposure and PFS was characterized using cox proportional hazard models. The final parameter estimates for relationship between binimetinib exposure as continuous variable and time to PFS were provided in Table 88 separately for each evaluated exposure metric. The baseline covariates retained in the final model after backward elimination were also provided in Table 88. No (nominally) statistically significant relationship was found between binimetinib exposure and time to PFS.

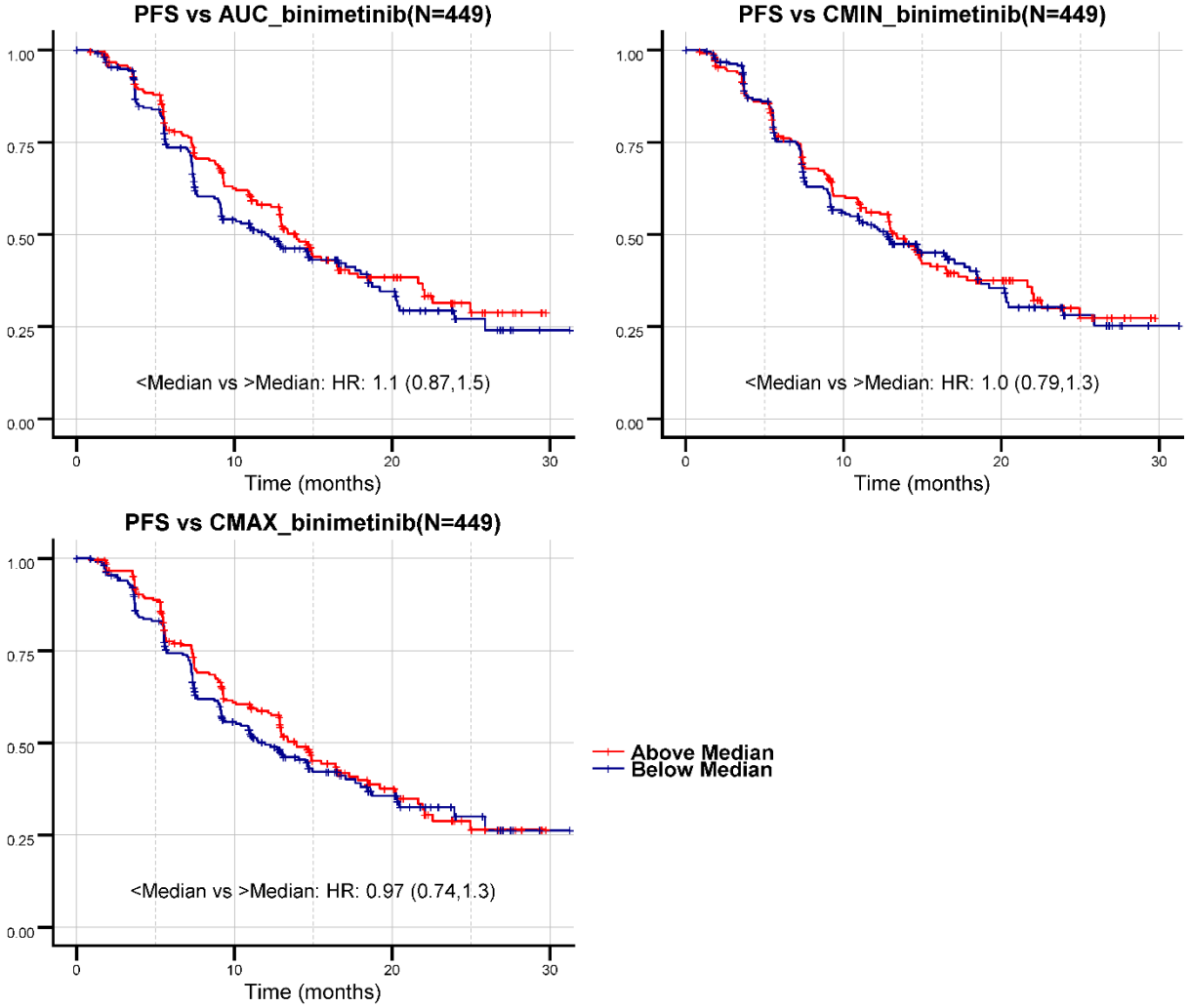
The effect of binimetinib exposure on PFS was also examined via Kaplan-Meier curves stratified by predicted SS binimetinib exposure quartile (Figure 26). After adjusting for significant covariate effects, the patients with low binimetinib exposure were estimated to have similar risk of progression or death compared to patients with high binimetinib exposure.

Table 88: Parameter Estimates of Final Binimetinib E-R Model of Time to PFS.

Covariate	HR	Lower 95% CI	Upper 95% CI	P-value
ECOG Score: 1	1.41	1.07	1.87	0.0162
Male vs Female	1.4	1.06	1.84	0.018
AUCinf	0.922	0.797	1.07	0.276
Log(Baseline LDH)	2.79	2.28	3.41	0
ECOG Score: 1	1.41	1.07	1.87	0.016
Male vs Female	1.41	1.07	1.85	0.0138
Cmin	0.0869	0.000814	9.26	0.305
Log(Baseline LDH)	2.8	2.29	3.42	0
ECOG Score: 1	1.4	1.06	1.86	0.0187
Male vs Female	1.41	1.06	1.86	0.0165
Cmax	0.68	0.249	1.86	0.451
Log(Baseline LDH)	2.77	2.26	3.39	0

Source: Reviewer's analysis based on dataset "adtte.xpt"

Figure 26: The Kaplan-Meier (KM) Curve of Time to PFS Stratified by Predicted Binimetinib Exposure Metrics.



Source: Reviewer's analysis based on dataset "adtte.xpt"

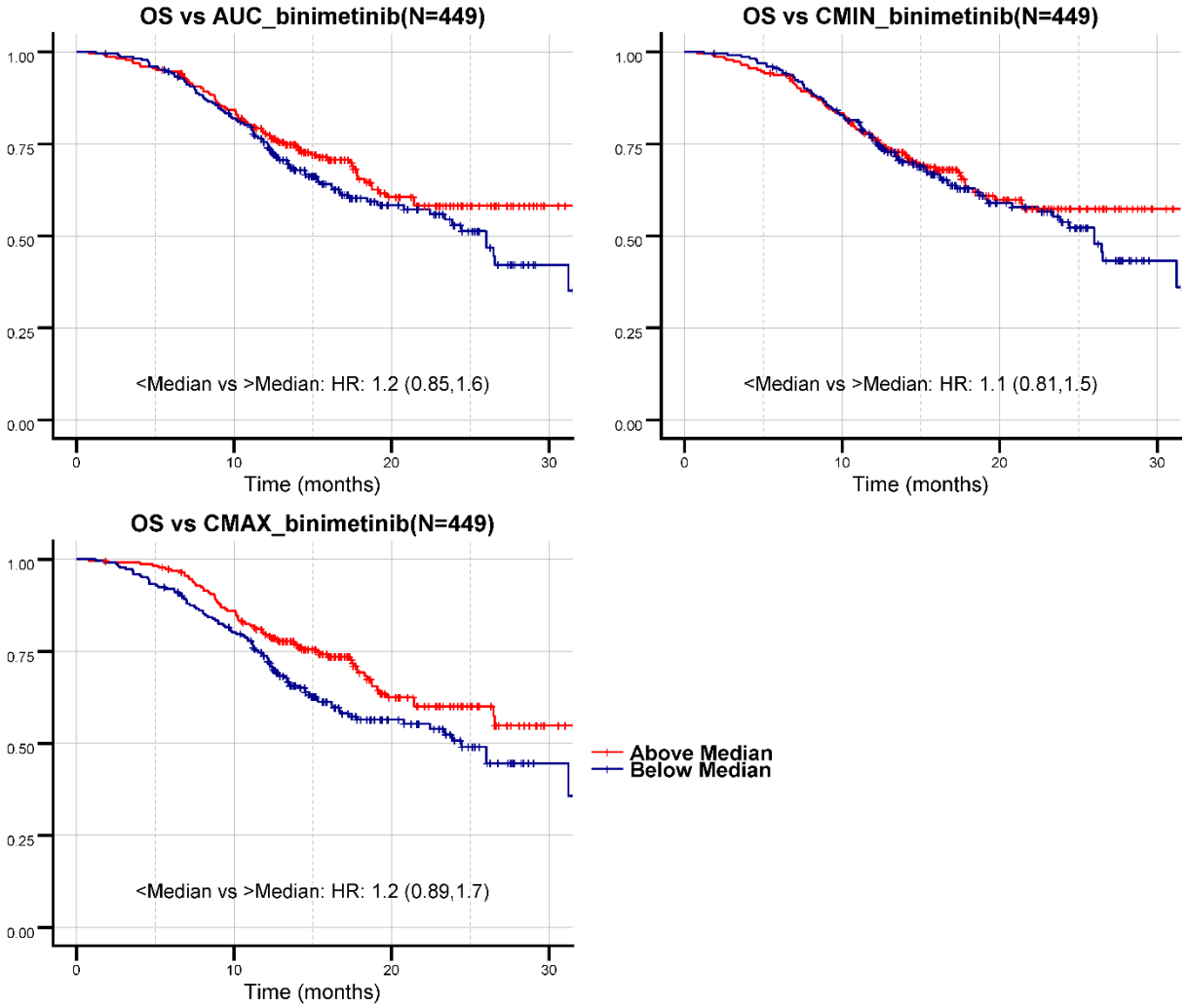
Similarly, the association between binimetinib exposure and OS was evaluated with Cox proportional hazard models. The final parameter estimates for relationship between binimetinib exposure as continuous variable and time to OS were provided in Table 89 separately for each evaluated exposure metric. A (nominally) statistically significant relationship was found between time to OS and binimetinib Cmax, but such relationships were not observed on Cmin and AUC. The Kaplan-Meier curves of time to OS in patients with low and high binimetinib exposure were provided in Figure 27. After adjusting for significant covariate effects, patients with low binimetinib exposure were estimated to have similar risks of death compared to patients with high binimetinib exposure, although the median OS is numerically longer in patients with high AUC or Cmax (Not reached vs 26 months).

Table 89: Parameter Estimates of Final Binimetinib E-R Model of Time to OS.

Covariate	HR	Lower 95% CI	Upper 95% CI	P-value
ECOG Score: 1	1.64	1.19	2.25	0.00255
AUCinf	0.879	0.734	1.05	0.158
Log(Baseline LDH)	2.91	2.35	3.6	0
ECOG Score: 1	1.69	1.22	2.33	0.00149
CMIN	0.24	0.000615	93.6	0.639
STAGE IIIC	0.144	0.0198	1.05	0.0554
STAGE IV M1A	0.622	0.334	1.16	0.134
STAGE IV M1B	0.975	0.604	1.57	0.918
STAGE IV M1C WITH ELEVATED LDH	0.76	0.48	1.2	0.24
Log(Baseline LDH)	3.1	2.32	4.16	2.88E-14
ECOG Score: 1	1.6	1.16	2.21	0.00426
CMAX	0.287	0.0869	0.946	0.0402
Log(Baseline LDH)	2.85	2.3	3.54	0

Source: Reviewer's analysis based on dataset "adsl.xpt"

Figure 27: The Kaplan-Meier (KM) Curve of Time to OS Stratified by Predicted Binimetinib Exposure Metrics.



Source: Reviewer's analysis based on dataset "adsl.xpt"

19.2.3.2 Binimetinib Exposure and Safety

The relationship between binimetinib exposure and time to safety endpoints was characterized using Cox proportional hazard models. The general safety endpoints and safety events of special interest were same as those evaluated in the dose-response analyses. The final parameter estimates for relationship between binimetinib AUC as continuous variable and time to safety endpoints were provided in Table 90 for general safety endpoints and in Table 91 for safety events of special interest. In general, no (nominally) statistically significant relationship was found between binimetinib AUC as continuous variable and time to evaluated safety events except for time to first dose adjustment/reduction. Patients with higher binimetinib exposure were more likely to experience dose adjustment/reduction based on the analysis.

The ER analyses also evaluated the effect of binimetinib exposure quartile on safety risks. Table 92 contains the rates of evaluated safety events in patients with binimetinib exposure below median and above median, as well as the HRs in safety risks comparing patients with low exposure to patients with high exposure. Based on the Cox regression analysis, patients with low binimetinib exposure had (nominally) significantly lower risks of experiencing dose adjustment/ reduction compared to patients with high binimetinib exposure. On the other hand, they have (nominally) significantly higher risks of experiencing serious adverse events and grade 2+ hand-foot syndrome compared to patients with high binimetinib exposure.

The risks of developing other safety events such as grade 2+ hemorrhage, grade 2+ rash, grade 2+ skin infections and QTcF> 450ms appear to be higher in patients with low binimetinib exposure, and the risks of developing liver toxicity and grade 1+ retinopathy excluding RVO appear to be higher in patients with high exposure, but their differences are not (nominally) statistically significant.

Table 90: Parameter Estimates of Final Binimetinib E-R Model of Time to Evaluated General Safety Event.

Covariate	HR	Lower 95% CI	Upper 95% CI	P-value
Time to first AE leading to discontinuation				
Age	1.03	1.01	1.06	0.00213
AUCinf	0.831	0.61	1.13	0.24
Time to first safety event of special interest for Encorafenib				
ECOG Score:1	0.662	0.485	0.904	0.00952
Europe	0.421	0.156	1.14	0.089
North America	0.874	0.301	2.54	0.804
Other	0.362	0.125	1.05	0.061
AUCinf	1.03	0.907	1.18	0.624
Time to first Grade 3/4 AE				
Age	1.01	1	1.02	0.0148
AUCinf	1.04	0.913	1.2	0.523
Log(Baseline LDH)	1.32	1.07	1.63	0.0102
Time to first SAE				
Age	1.02	1.01	1.03	0.00524
AUCinf	0.948	0.777	1.16	0.595
Log(Baseline LDH)	1.86	1.45	2.37	7.87E-07
Time to first dose adjustment/reduction				
BRAF:V600E	0.632	0.452	0.885	0.00745
AUCinf	1.14	1.01	1.27	0.0292

Source: Reviewer's analysis based on dataset "adttes.xpt"

Table 91: Parameter Estimates of Final Binimetinib E-R Model of Time to Evaluated Safety Event of Special Interest.

Covariate	HR	Lower 95% CI	Upper 95% CI	P-value
Time to AST > 5x ULN or ALT > 5x ULN				
BRAF:V600E	0.251	0.101	0.624	0.00292
Europe	0.0426	0.0088	0.206	8.75E-05
North America	0.124	0.0188	0.817	0.03
Other	0.152	0.0278	0.837	0.0304
AUCinf	1	0.991	1.01	0.938
STAGE IIIC	1.64	0.349	7.75	0.53
STAGE IV M1A	0.976	0.3	3.17	0.968
STAGE IV M1B	0.838	0.285	2.47	0.749
STAGE IV M1C WITH ELEVATED LDH	0.0319	0.0032	0.319	0.00336
Log(Baseline LDH)	3.03	1.34	6.82	0.00762
Time to First Grade 2 or above Hemorrhage				
AUCinf	0.998	0.986	1.01	0.782
Log(Baseline LDH)	3.8	2.04	7.09	2.61E-05
Time to First Grade 2 or above Myopathy				
AUCinf	0.998	0.988	1.01	0.757
Time to First Grade 2 or above Hand-Foot Syndrome				
AUCinf	0.974	0.92	1.03	0.359
Time to First Grade 2 or above Rash				
Non-Caucasian vs Caucasian	3.64E-08	0	Inf	0.996
AUCinf	1	0.991	1.01	0.984
Time to First Grade 1 or above Retinopathy Excluding RVO				
ECOG Score: 1	0.606	0.413	0.89	0.0107
Europe	0.398	0.126	1.26	0.117
North America	0.891	0.261	3.04	0.853
Other	0.277	0.079	0.969	0.0446
Male vs Female	1.45	1.03	2.04	0.0313
AUCinf	0.999	0.995	1	0.765
Weight	0.986	0.976	0.996	0.00587
Time to First Grade 2 or above Skin Infections				
Metastatic Disease	0.178	0.052	0.611	0.00606
Primary Site: Unknown	3.58E-08	0	Inf	0.996
AUCinf	0.992	0.978	1.01	0.317
Log(Baseline LDH)	2.25	1.33	3.8	0.00254
Time to Definitive Deterioration in LVEF				
AUCinf	1	1	1.01	0.0519
Weight	1.01	1	1.02	0.0431
Time to First QTcF Increase from baseline>30 ms				
Age	1.02	1.01	1.04	0.00522
AUCinf	1	0.996	1	0.804

STAGE IIIC	1.56	0.592	4.14	0.367
STAGE IV M1A	2.04	1.13	3.68	0.0177
STAGE IV M1B	1.83	1.05	3.2	0.0323
STAGE IV M1C WITH ELEVATED LDH	2.43	1.49	3.97	0.000391
Time to First new QTcF>450 ms				
Age	1.03	1.01	1.05	0.00271
Metastatic Disease	0.0109	0.00222	0.0533	2.47E-08
AUCinf	1	0.997	1.01	0.387
STAGE IIIC	0.00351	0.000227	0.0544	5.25E-05
STAGE IV M1A	0.997	0.442	2.25	0.995
STAGE IV M1B	0.888	0.414	1.9	0.76
STAGE IV M1C WITH ELEVATED LDH	1.82	1.01	3.28	0.0451

Source: Reviewer's analysis based on dataset "adttes.xpt"

Table 92: The Rates of Evaluated Safety Events in Patients with Low or High Binimetinib Exposure and the HR in Risks Comparing Patients with Low Exposure to Patients with High Exposure.

Evaluated Time-to-Event	Rates		HR (Below Median vs Above Median)
	AUC Below Median N=225, n(%)	AUC Above Median N=224, n(%)	
Overall Safety			
AE Leading to Discontinuation	29 (12.9)	30 (13.4)	1.3 (0.74, 2.2)
Special Interest of Encorafenib	119 (52.9)	127 (56.7)	0.9 (0.7, 1.2)
Grade 3/4 AE	116 (51.6)	114 (50.9)	1.0 (0.8, 1.4)
SAE	74 (32.9)	61 (27.2)	1.5 (1.0, 2.1)
First Dose Adjustment/Reduction	112 (49.8)	143 (63.8)	0.73 (0.57, 0.93)
Safety of Special Interest			
AST/ALT > 5x ULN	10 (4.52)	15 (6.79)	0.71 (0.31, 1.6)
Grade 2+ Myopathy	12 (5.33)	12 (5.36)	1.1 (0.48, 2.4)
Grade 2+ Hemorrhage	9 (4.0)	6 (2.68)	1.6 (0.55, 4.4)
Grade 2+ Hand-Foot Syndrome	11 (4.89)	2 (0.89)	5.9 (1.3, 27)
Grade 2+ Rash	17 (7.56)	11 (4.91)	1.5 (0.7, 3.2)
Grade 1+ Retinopathy Excluding RVO	80 (35.6)	93 (41.5)	0.87 (0.63, 1.2)
Grade 2+ Skin Infections	19 (8.44)	11 (4.91)	1.8 (0.87, 3.9)
Definitive Deterioration in LVEF	67 (30.3)	63 (28.6)	1.2 (0.82, 1.6)
First QTcF Increase from baseline>30ms	60 (27.0)	51 (23.8)	1.4 (0.95, 2.1)
First new QTcF>450ms	34 (16.3)	31 (14.8)	1.5 (0.88, 2.5)

Source: Reviewer's analysis based on dataset "adttes.xpt"

In summary, DR relationships for efficacy suggest that encorafenib 450mg and 300mg QD in combination therapy have a comparable ORR and PFS. However, OS appears to be better in encorafenib dosing regimen 450mg QD compared to 300mg QD in combination with

binimetinib based on preliminary analyses. Therefore, there is insufficient evidence that Combo 300 is as effective as Combo 450. Cross-part comparison of safety profile between Combo 300 and Combo 450 did not indicate a clinically significant safety concern for Combo 450 relative to Combo 300 which would outweigh the potential for improved efficacy in higher dose. The ER relationships were consistent with DR relationships, and they both support the use of the proposed encorafenib dose of 450 mg QD with dose modification in the event of adverse reactions to the lowest dose of 200 mg.

19.3. Statistical Appendix

Patient Disposition

The encorafenib (Part 1) arm had 17% of patients with treatment ongoing, compared to 26% ongoing in the encorafenib (Part 2) arm and 39% in the Combo 300 arm. However, patients in Part 1 also had a longer duration of follow up, as discussed in "Other Endpoints". Table 93 shows the patient disposition of Part 2, including the pooled Encorafenib group.

Table 93: Patient Disposition in Part 2 of COLUMBUS, including pooled Encorafenib Group

	Encorafenib (Part 1)	Encorafenib (Part 2)	Encorafenib (Parts 1 + 2)	Encorafenib 300mg + Binimetinib
N	194	86	280	258
Treatment received (%)				
YES	192 (99)	84 (98)	276 (99)	257 (100)
NO	2 (1)	2 (2)	4 (1)	1 (0)
Primary reason for treatment discontinuation (%)				
ADVERSE EVENT	26 (13)	6 (7)	32 (11)	22 (9)
DEATH	1 (1)	1 (1)	2 (1)	8 (3)
LOST TO FOLLOW-UP	0 (0)	1 (1)	1 (0)	0 (0)
PHYSICIAN DECISION	21 (11)	8 (9)	29 (10)	22 (9)
PROGRESSIVE DISEASE	95 (49)	39 (45)	134 (48)	96 (37)
PROTOCOL DEVIATION	1 (1)	0 (0)	1 (0)	0 (0)
SUBJECT/GUARDIAN DECISION	15 (8)	7 (8)	22 (8)	8 (3)
UNTREATED	2 (1)	2 (2)	4 (1)	1 (0)
TREATMENT ONGOING	33 (17)	22 (26)	55 (20)	101 (39)
Treatment ongoing (%)				
YES	33 (17)	22 (26)	55 (20)	101 (39)
NO	159 (82)	62 (72)	221 (79)	156 (60)
UNTREATED	2 (1)	2 (2)	4 (1)	**1 (0)**

Source: FDA Analysis

Demographics

Table 94 shows the patient demographics in the analysis set used for Test 3 of COLUMBUS, which includes patients randomized to encorafenib in Part 1. Due to the addition of patients from the encorafenib arm in Part 1, the encorafenib (Parts 1 + 2) group had a lower percentage of patients aged 65 and older (24%) than the Combo 300 arm (32%). There was also a higher percentage of women (46%) in the encorafenib (Parts 1 + 2) group than in the Combo 300 arm (41%). Otherwise, the demographics appear to be generally balanced over the two arms.

Table 94: Patient Demographics in Part 2 of COLUMBUS, including Pooled Encorafenib Group

	Encorafenib (Part 1)	Encorafenib (Part 2)	Encorafenib (Parts 1 + 2)	Combo 300
N	194	86	280	258
Age (mean (sd))	54.6 (12.6)	55.8 (14.7)	55.0 (13.3)	57.4 (14.0)
Age Category (%)				
<65	154 (79)	60 (70)	214 (76)	175 (68)
>=65	40 (21)	26 (30)	66 (24)	83 (32)
Sex (%)				
F	86 (44)	42 (49)	128 (46)	107 (41)
M	108 (56)	44 (51)	152 (54)	151 (59)
Race (%)				
MISSING	1 (1)	1 (1)	2 (1)	0 (0)
AMERICAN INDIAN OR ALASKA NATIVE	2 (1)	0 (0)	2 (1)	0 (0)
ASIAN	6 (3)	7 (8)	13 (5)	15 (6)
BLACK OR AFRICAN AMERICAN	0 (0)	0 (0)	0 (0)	1 (0)
OTHER	2 (1)	0 (0)	2 (1)	2 (1)
UNKNOWN	9 (5)	0 (0)	9 (3)	4 (2)
WHITE	174 (90)	78 (91)	252 (90)	236 (91)
ECOG (%)				
0	143 (74)	62 (72)	205 (73)	191 (74)
1	51 (26)	24 (28)	75 (27)	67 (26)

Source: FDA Analysis

Protocol Deviations

Table 95 shows the protocol deviations in the analysis set used for Test 3 of COLUMBUS, which includes patients randomized to encorafenib in Part 1.

Table 95: Protocol Deviations in Part 2 of COLUMBUS, including pooled Encorafenib Group

Reason	Encorafenib (Part 1)	Encorafenib (Part 2)	Encorafenib (Parts 1 + 2)	Combo 300
N	192	194	191	
Patient did not receive at least one dose of study medication	2 (1)	2 (2)	4 (1)	1 (0)
No histologically confirmed diagnosis of unresectable or metastatic cutaneous melanoma or unknown primary melanoma (stage IIIb, IIIC to IV per AJCC)	1 (1)	0 (0)	1 (0)	0 (0)
Not positive for *BRAF V600* mutation	2 (1)	0 (0)	2 (1)	0 (0)
Prior treatment for unresectable or metastatic cutaneous melanoma other than immunotherapy	0 (0)	0 (0)	0 (0)	2 (1)
Prior treatment with a RAF and/or MEK inhibitor	1 (1)	0 (0)	1 (0)	0 (0)
New anti-neoplastic therapy administered after start of study treatment and prior to first tumor assessment	4 (2)	0 (0)	4 (1)	0 (0)

Source: FDA Analysis

Durability of Response

Table 96: Confirmed ORR and DOR Results from Part 2 of COLUMBUS (Combo 450 vs. Pooled Encorafenib Group)

	Combo 300 N = 258	Encorafenib (Parts 1 + 2) N = 280
ORR[1]	66%	50%
(95% CI)[2]	(60%, 72%)	(44%, 56%)
CR	8%	5%
PR	58%	45%
Median DOR, months	12.7	12.9
(95% CI)	(9.3, 15.1)	(8.9, 15.5)

Source: FDA Analysis
[1] BIRC central review
[2] Estimated using the Clopper-Pearson method

Additional Exploratory Analyses Conducted on the Individual Trial

Array pre-specified a sensitivity analysis for PFS that would repeat the primary analysis using the BIRC data on the Per Protocol set. Table 97 summarizes these results in the Combo 450 vs. encorafenib comparison.

Table 97: Progression-Free Survival in the Per-Protocol Population for Part 1 of COLUMBUS (Combo 450 vs. Encorafenib)

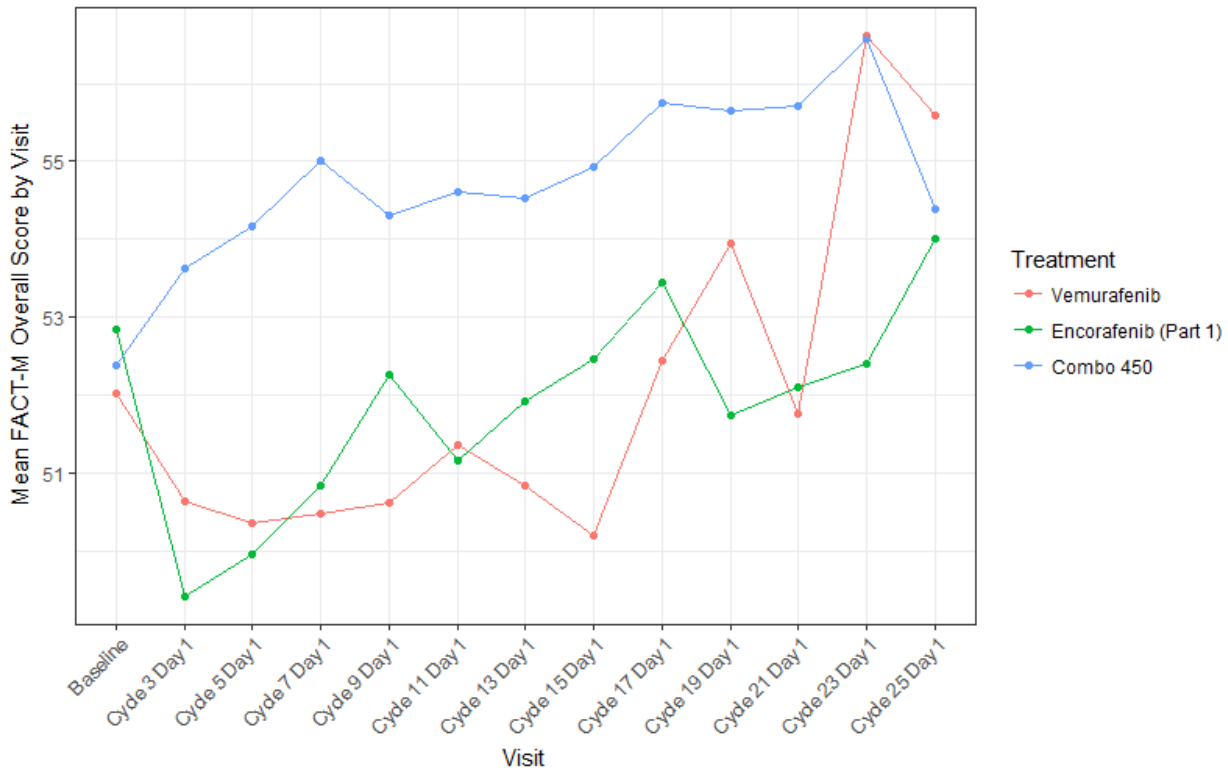
	Encorafenib N = 184	**Combo 450 N = 188**
Number of events (%)	95 (52)	95 (51)
Censored (%)	89 (48)	93 (49)
Median PFS in months (95% CI)	9.6 (7.5, 14.8)	15.5 (11.0, 18.7)
Hazard Ratio (95% CI)[1]	0.73 (0.54, 0.97)	

Source: FDA Analysis
[1] Estimated with the Cox proportional hazards model stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs. IVM1c) and ECOG score (0 vs. 1).

Secondary or Exploratory COA (PRO) Endpoints

The mean FACT-M overall score by treatment arm and visit in Part 1 is shown in Figure 28.

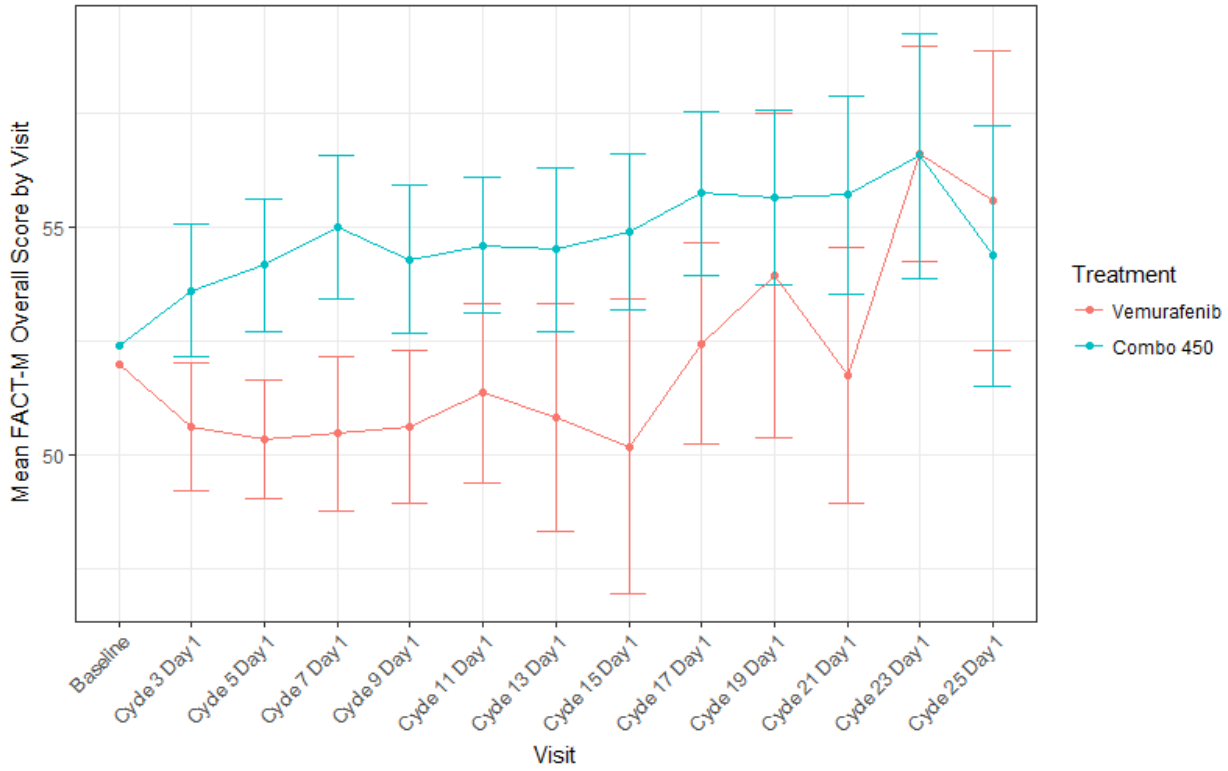
Figure 28: Mean FACT-M Overall Score by Treatment Arm and Visit in Part 1



Source: FDA Analysis

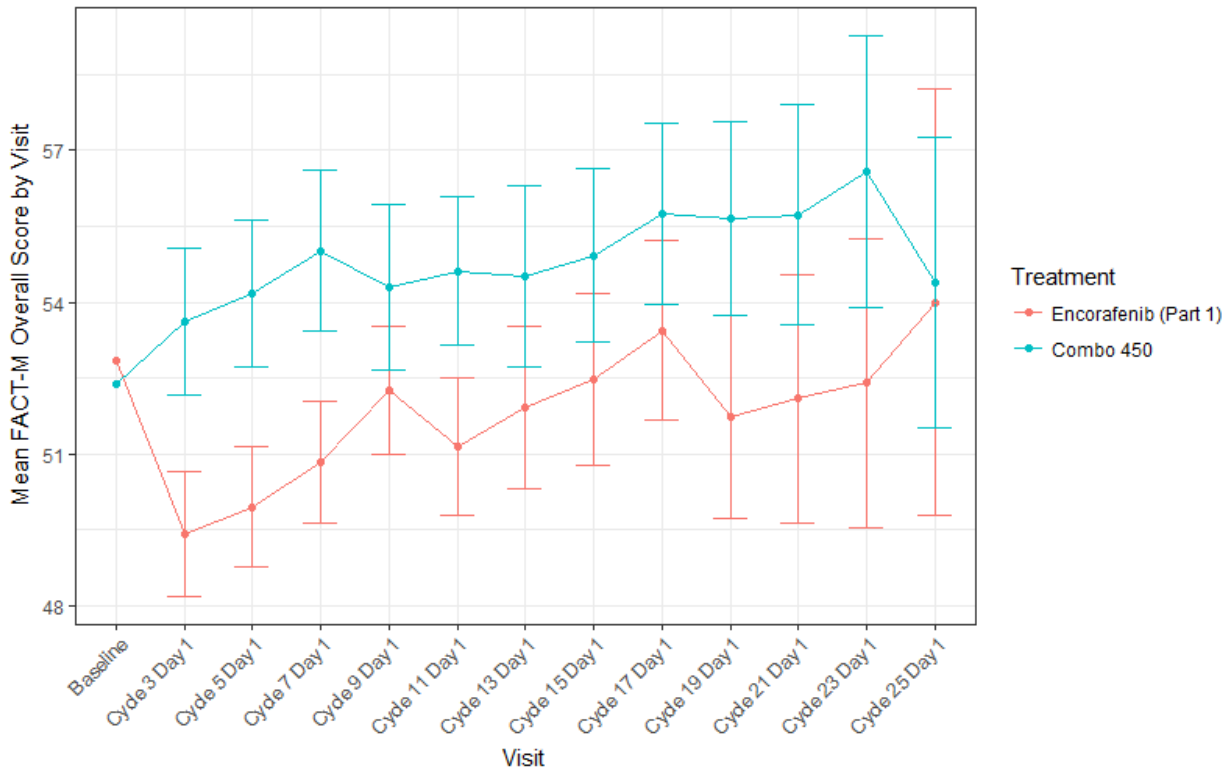
Figure 29 and Source: FDA Analysis.
Figure 30 show these means for Combo 450 vs. vemurafenib and Combo 450 vs. encorafenib. A 95% confidence interval for each visit is plotted about the mean.

Figure 29: Mean FACT-M Overall Score by Treatment Arm and Visit in Part 1 (Combo 450 vs. Vemurafenib)



Source: FDA Analysis.

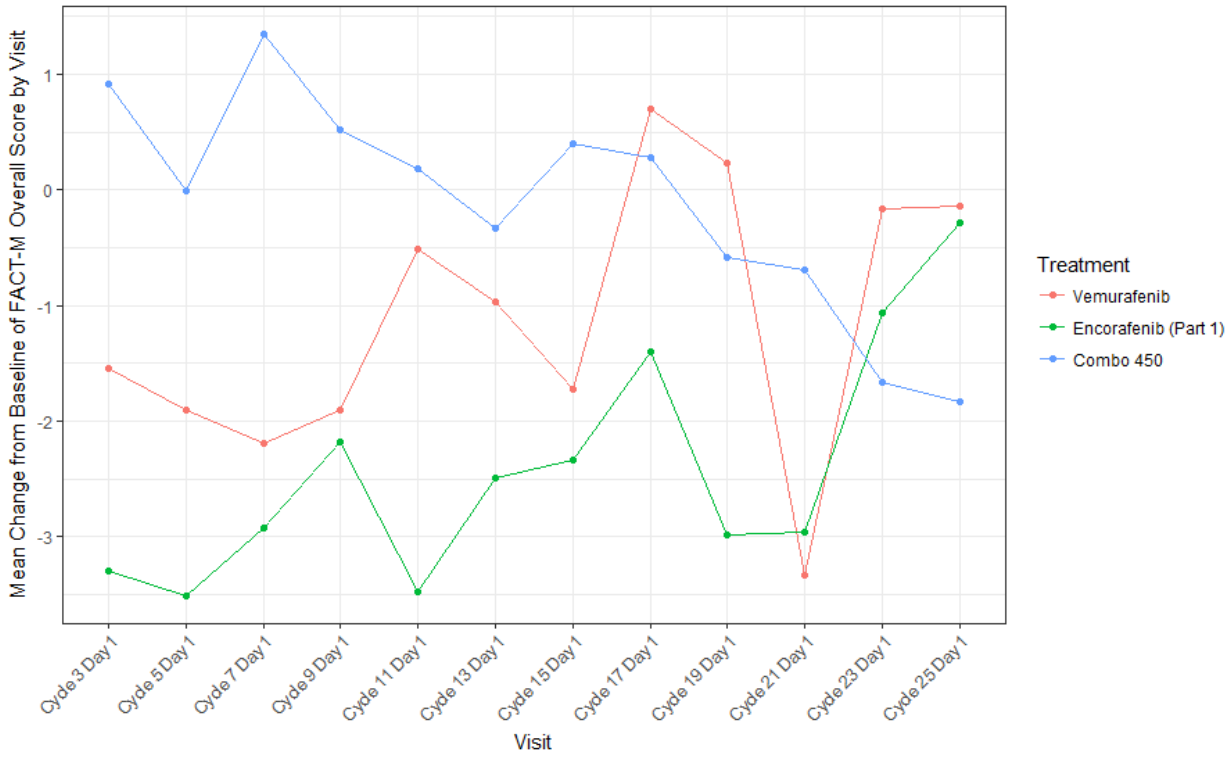
Figure 30: Mean FACT-M Overall Score by Treatment Arm and Visit in Part 1 (Combo 450 vs. Encorafenib)



Source: FDA Analysis

The mean change from baseline in FACT-M overall score by treatment arm and visit in Part 1 is shown in Figure 31.

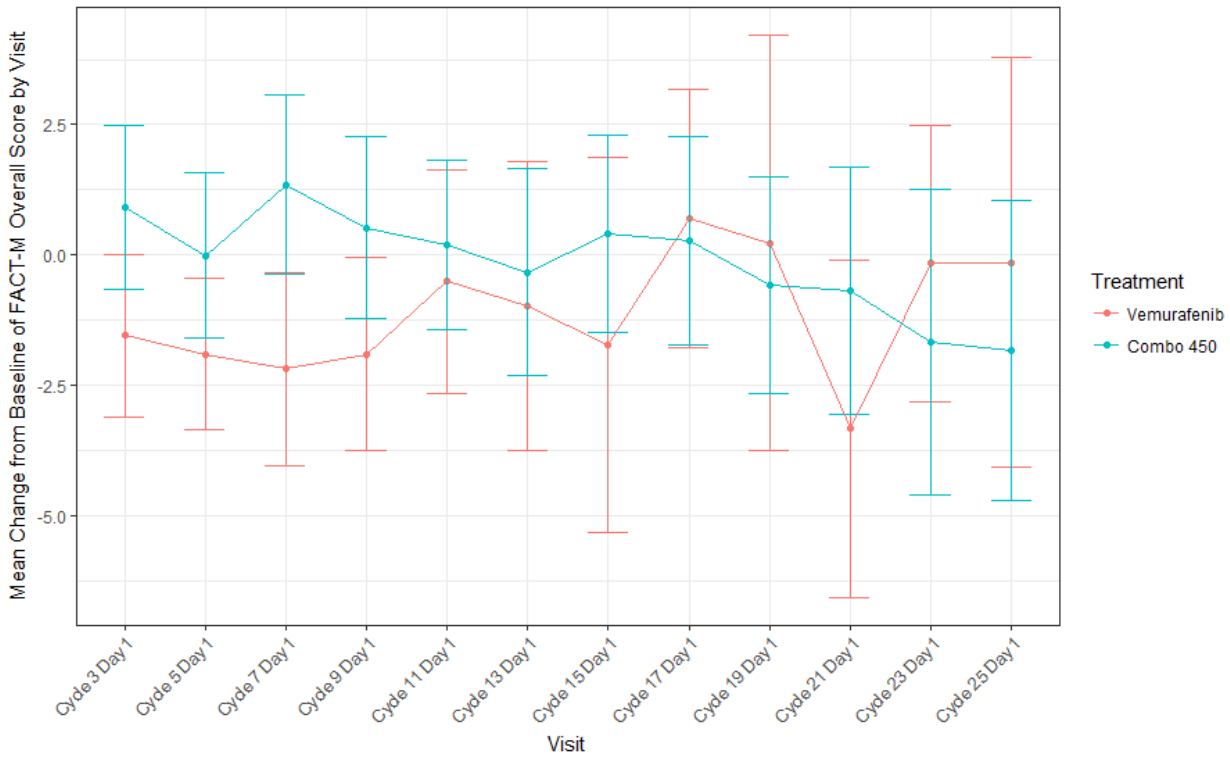
Figure 31: Mean Change from Baseline FACT-M Overall Score by Treatment Arm and Visit in Part 1



Source: FDA Analysis

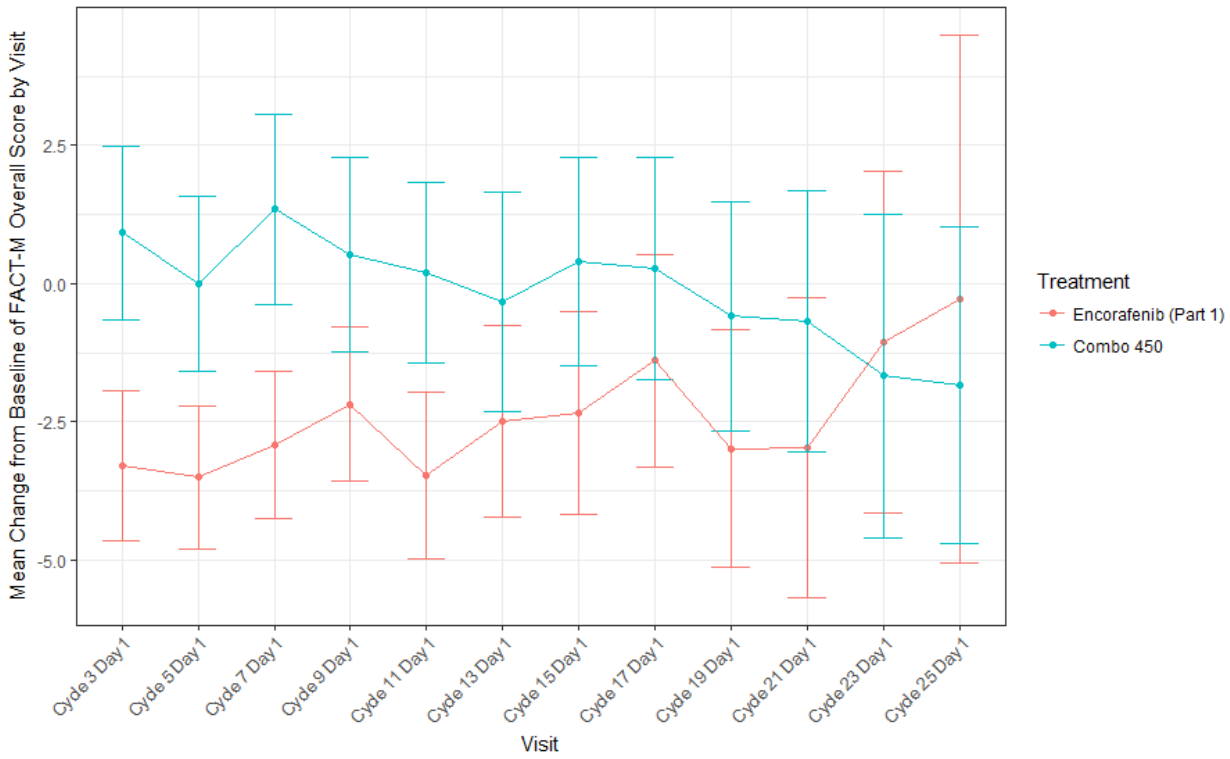
Figure 32 and Source: FDA Analysis
Figure 33 show these means for Combo 450 vs. vemurafenib and Combo 450 vs. encorafenib. A 95% confidence interval for each visit is plotted about the mean.

Figure 32: Mean Change from Baseline FACT-M Overall Score by Treatment Arm and Visit in Part 1 (Combo 450 vs. Vemurafenib)



Source: FDA Analysis

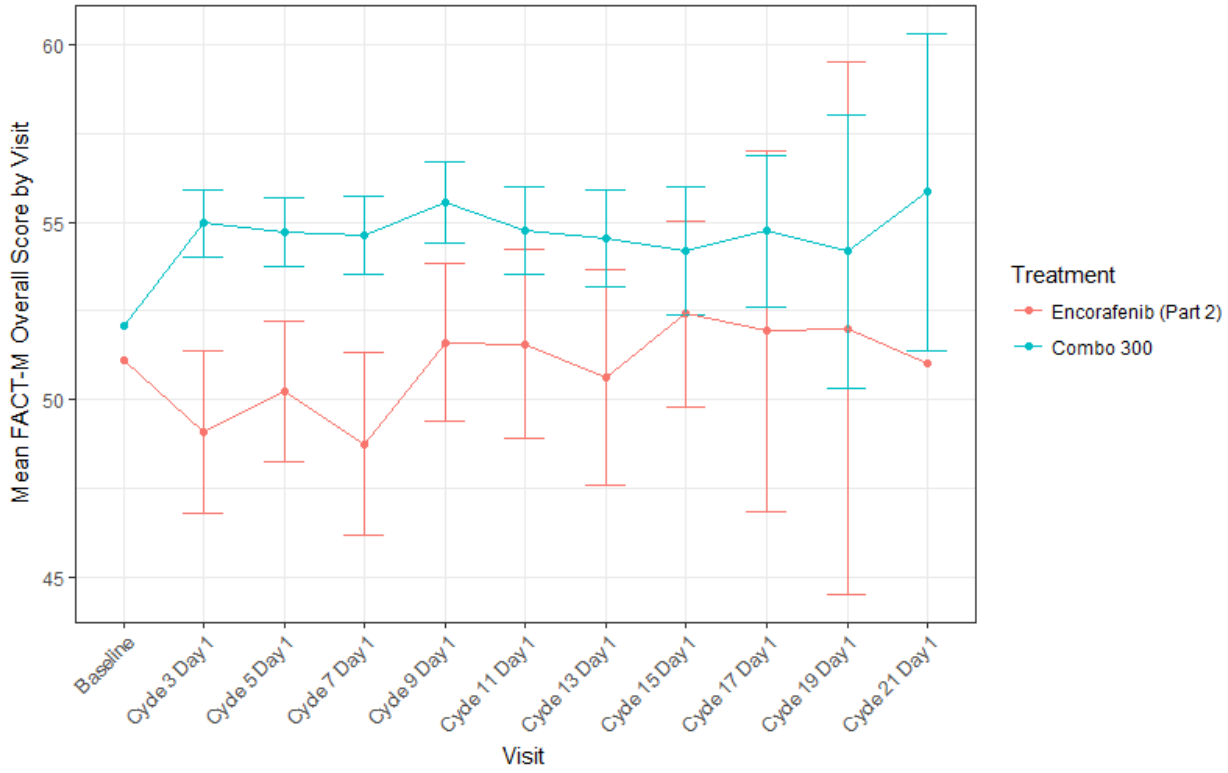
Figure 33: Mean Change from Baseline FACT-M Overall Score by Treatment Arm and Visit in Part 1 (Combo 450 vs. Encorafenib)



Source: FDA Analysis

The mean FACT-M overall score by treatment arm and visit in Part 2 is shown in Figure 34.

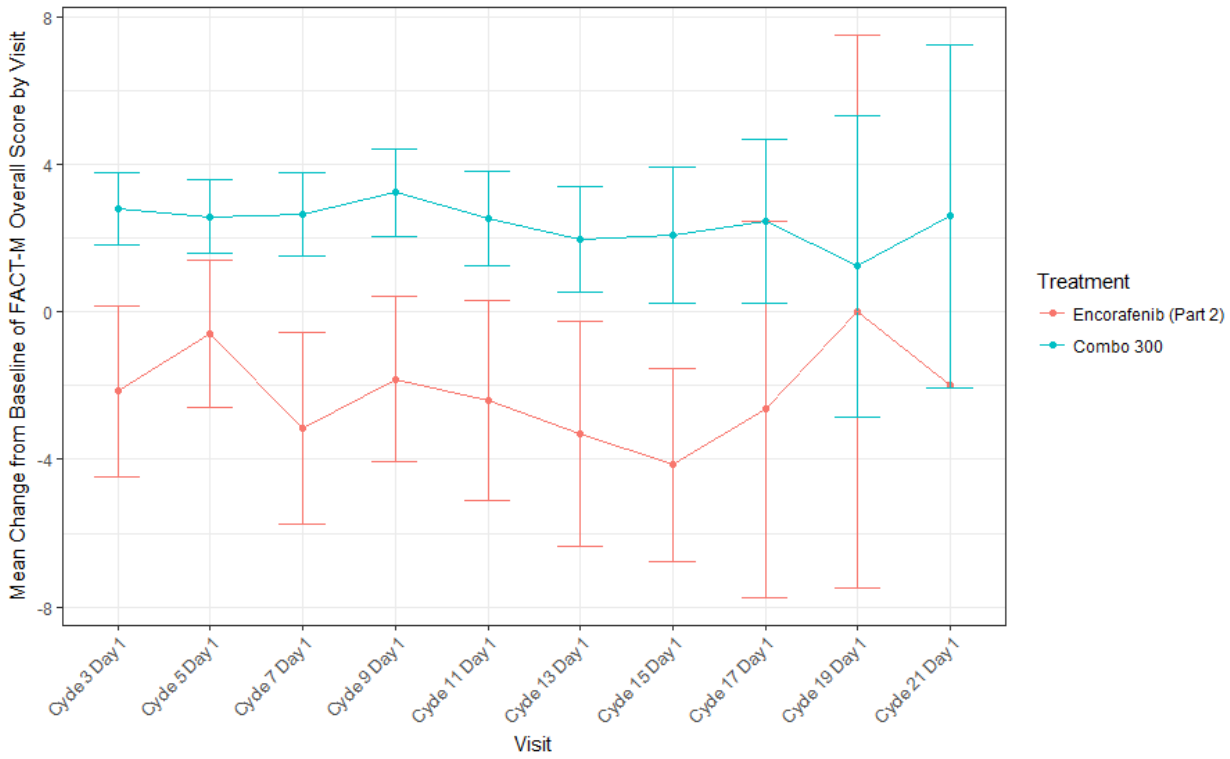
Figure 34: Mean FACT-M Overall Score by Treatment Arm and Visit in Part 2 (Combo 300 vs. Encorafenib)



Source: FDA Analysis

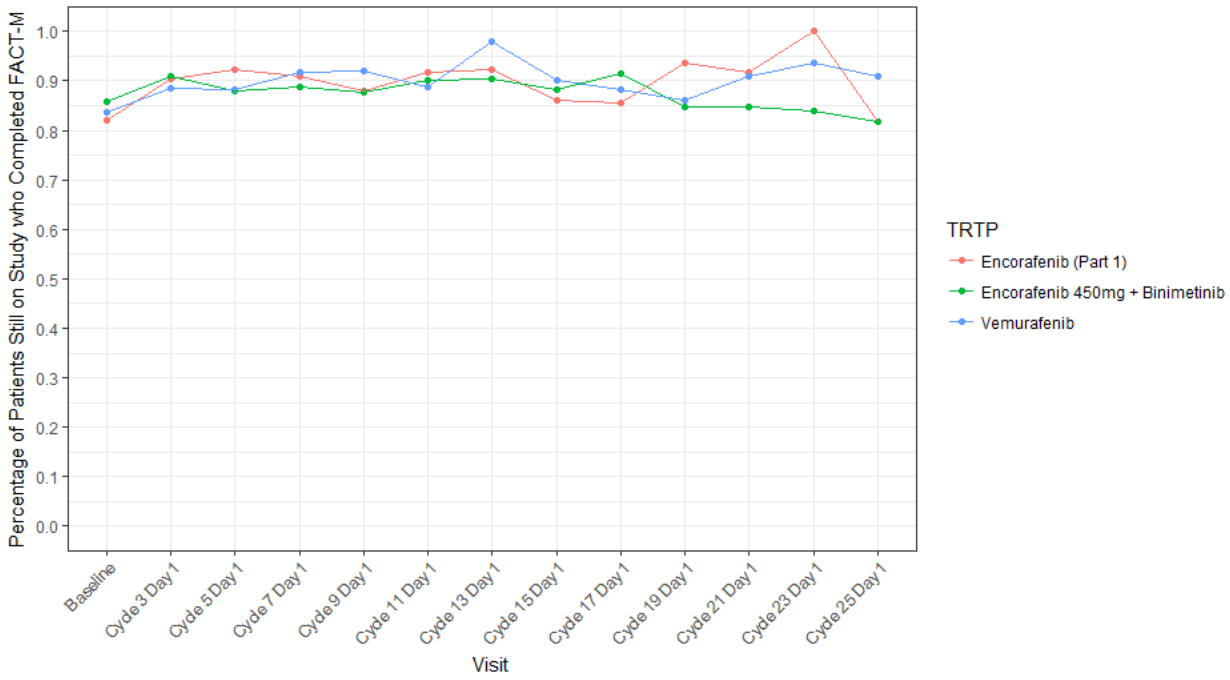
The mean change from baseline in FACT-M overall score by treatment arm and visit in Part 2 is shown in Figure 35.

Figure 35: Mean Change from Baseline FACT-M Overall Score by Treatment Arm and Visit in Part 2 (Combo 300 vs. Encorafenib)



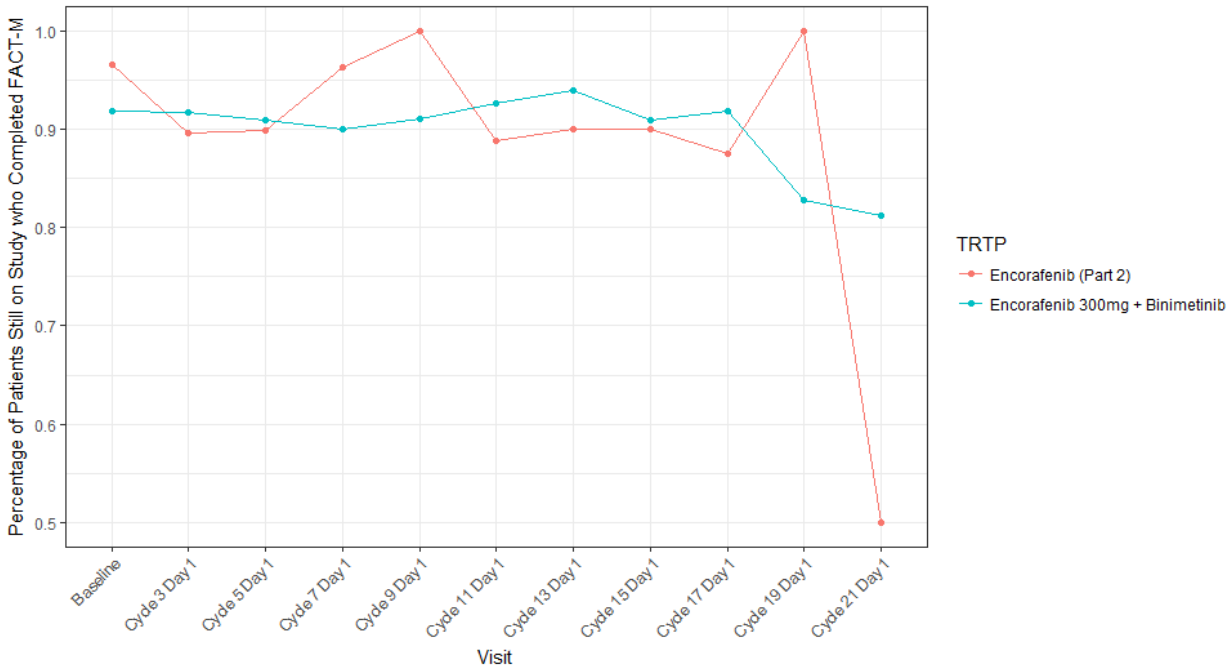
Source: FDA Analysis

Figure 36: FACT-M Compliance Summary by Time Window and Treatment (Part 1)



Source: FDA Analysis

Figure 37: FACT-M Compliance Summary by Time Window and Treatment (Part 2)



Source: FDA Analysis

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/s/

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