NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project Orbis. FDA collaborated with Health Canada (HC). While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agency.

In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	sNDA
Application Number(s)	210496/017
Priority or Standard	Priority
Submit Date(s)	July 1, 2024
Received Date(s)	July 1, 2024
PDUFA Goal Date	January 1, 2025
Division/Office	Division of Oncology 3 / Office of Oncologic Diseases
Review Completion Date	See DAARTS stamp
Established Name	encorafenib
(Proposed) Trade Name	Braftovi
Pharmacologic Class	Kinase inhibitor
Code name	LGX-818
Applicant	Array BioPharma, Inc., a wholly owned subsidiary of Pfizer
Formulation(s)	capsule
Dosing Regimen	300 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	BRAFTOVI is indicated, in combination with cetuximab and mFOLFOX6, for the treatment of patients with metastatic colorectal cancer (CRC) with a *BRAF V600E* mutation, as detected by an FDA-approved test
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	BRAFTOVI is indicated, in combination with cetuximab and mFOLFOX6, for the treatment of patients with metastatic colorectal cancer (mCRC) with a *BRAF V600E mutation*, as detected by an FDA-approved test This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

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Project Orbis #135 Partners

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Lead Clinical Reviewer	(b) (6)
Biostatistics Reviewer	
Senior Regulatory Project Manager	
Regulatory Project Manager	
Label Reviewer	

Glossary

1L	first line
5-FU	5-fluorouracil
A	Asian
AA	accelerated approval
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AI	American Indian
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AN	Alaska Native
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC_{last}	area under the concentration-time curve
B	Black
BDR	blind data review
BICR	blinded independent central review
BID	twice a day
BLA	biologics license application

BOR	best overall response
BPCA	Best Pharmaceuticals for Children Act
BPM	beats per minute
BRAF	B-Raf proto-oncogene, serine/threonine-protein kinase
BRAF	serine/threonine-protein B-Raf
BRAFi	serine/threonine-protein B-Raf inhibitor
BRF	benefit risk framework
BSC	best supportive care
BTD	breakthrough therapy designation
BTDR	breakthrough therapy designation request
CAP	College of American Pathologists
CAPOX	capecitabine/oxaliplatin
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CDx	companion diagnostic
CEA	carcinoembryonic antigen
cfDNA	circulating free DNA
ctDNA	circulating tumor DNA
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	clinical laboratory improvement amendments
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer

CRF	case report form
CRO	contract research organization
CRP	c-reactive protein
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
ctMONiTR	ctDNA for monitoring treatment response
CYP	cytochrome P450 enzyme 3A4
d	day
D5W	dextrose 5% in water
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
DMC	data monitoring committee
dMMR	DNA mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
EC	encorafenib plus cetuximab
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCTD	electronic common technical document
E-DMC	external data monitoring committee
EGFR	epidermal growth factor receptor
EP	endpoint
ER	exposure-response
ERK	extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
ETASU	elements to assure safe use
EU	European Union

EUCTR	European Union Clinical Trials Register
EQDD	enhanced quantitative drug development
F	female
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FOLFIRI	5-fluorouracil/leucovorin (folic acid)/irinotecan
FOLFOX	5-fluorouracil/leucovorin (folic acid)/oxaliplatin
FOLFOXIRI	5-fluorouracil/leucovorin (folic acid)/oxaliplatin/irinotecan
FU	fluorouracil
GCP	good clinical practice
GI	gastrointestinal
GLP	good laboratory practice
GRMP	good review management practice
HLT	high lactate threshold
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
IA	interim analysis
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IFL	irinotecan, fluorouracil, and leucovorin
IND	investigational new drug
iPSP	initial pediatric study plan
IRB	Institutional Review Board
IRT	interactive response technology
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

IV	intravenous
JSMO	Japanese Society of Medical Oncology
K-M	Kaplan–Meier
KRAS	KRAS proto-oncogene, GTPase
LFT	liver function test
LV	leucovorin
M	male
mCRC	metastatic colorectal cancer
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase kinase
mFOLFOX6	modified 5-fluorouracil/leucovorin/oxaliplatin
mITT	modified intent to treat
MMR	mismatch repair
mo	month
MR	multiracial
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
mTPP	median time to progression
N	number
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCT	National Clinical Trial
NDA	new drug application
NGS	next generation sequencing
NME	new molecular entity
NR	not reached/not reported
NRAS	NRAS proto-oncogene, GTPase
NSCLC	non-small cell lung cancer

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OR	objective response
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PADER	Periodic Adverse Drug Experience Report
PBRER	Periodic Benefit-Risk Evaluation Report
PCD	primary completion date
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death 1 ligand 1
PFS	progression-free survival
PH3	phase 3
PI	prescribing information
PK	pharmacokinetic(s)
PMA	premarket approval
PMAR	population modeling analysis report
PMC	postmarketing commitment
pMMR	proficient mismatch repair
popPK	population pharmacokinetic
PMR	postmarketing requirement
PO	oral
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome

PSUR	periodic safety update report
PT	preferred term
Q1	quartile 1
Q2W	every 2 weeks
Q3	quartile 3
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
QD	once daily
QT	QT interval
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QW	once every week
RAF	RAF family of proto-oncogenes
RAF	RAF GTPase
RAS	rat sarcoma viral oncogene homologue
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RP2D	recommended phase 2 dose
RTOR	real-time oncology review
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGE	special government employee
SLI	safety lead-in
SmPC	summary of product characteristics
sNDA	supplemental new drug application
SOC	system organ class
STDM	study data tabulation model

TBILI	total bilirubin
TEAE	treatment emergent adverse event
TTP	time to progression
TTR	time to response
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
W	White
WBC	white blood cell
WHO	World Health Organization
WRO	written response only
wk	week
WT	wild type

1 Executive Summary

1.1. **Product Introduction**

Encorafenib is a kinase inhibitor that targets cancers with *BRAF V600E* mutations, the most common of the known *BRAF* mutations.

Encorafenib is approved for the following indications:

- in combination with binimetinib for the treatment of adult patients with metastatic non-small cell lung cancer with a *BRAF V600E* mutation, as detected by an FDA-approved test.
- in combination with binimetinib for the treatment of patients with unresectable or metastatic melanoma with a *BRAF V600E* or *V600K* mutation, as detected by an FDA-approved test.
- in combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer (mCRC) with a *BRAF V600E* mutation, as detected by an FDA-approved test.

Encorafenib is supplied as 75 mg hard gelatin capsules for oral use. The proposed dosage regimen is 300 mg (four 75 mg capsules) orally once daily in combination with cetuximab until disease progression or unacceptable toxicity.

The Applicant's proposed indication is as follows:

> "Braftovi is indicated, in combination with cetuximab and mFOLFOX6, for the (b) (4) treatment of patients with metastatic colorectal cancer (mCRC) with a *BRAF V600E* mutation, as detected by an FDA-approved test."

1.2. **Conclusions on the Substantial Evidence of Effectiveness**

Substantial evidence of effectiveness was established via the results of one adequate and well controlled clinical investigation [BREAKWATER trial (NCT04607421)] plus confirmatory evidence (BEACON CRC; NCT02928224) in a later line CRC setting. The BREAKWATER trial is described below. BEACON CRC is already described in product labeling.

The recommendation for accelerated approval is based on the results of the BREAKWATER trial (Study C4221015), a randomized, active-controlled, open-label, trial evaluating adult patients with *BRAF V600E* mutation-positive mCRC who have not received prior therapy for the treatment of metastatic disease. The efficacy population consisted of 220 patients randomized 1:1 to treatment with either encorafenib administered at a dose of 300 mg orally daily in combination with cetuximab and mFOLFOX6 (EC + mFOLFOX6) or to standard of care chemotherapy that included mFOLFOX6, FOLFOXIRI, or CAPOX each with or without bevacizumab (control arm). The primary study objective was to demonstrate superiority of EC + mFOLFOX6 compared to chemotherapy via objective response rate (ORR) per RECIST v1.1 as assessed by

blinded independent central review (BICR). A key secondary objective was to evaluate the duration of response (DOR).

The BREAKWATER trial demonstrated a BICR-ORR of 61% [95% CI: 51.6, 69.5] and a median DOR of 13.9 months [95% CI: 8.5, NE] in the EC+mFOLFOX6 Arm compared to a BICR-ORR of 40% [95% CI: 31.3, 49.3] and a median DOR of 11.1 months [95% CI: 6.7, 12.7] in the Control Arm. These results are considered clinically meaningful when considering that this is a patient population with a serious and life-threatening disease and responses observed on this study are substantially better than what has been observed with available therapies. Supportive data demonstrating the necessity of the addition of mFOLFOX6 to encorafenib and cetuximab for the observed treatment effect is provided by the analysis of the EC-alone Arm. In 158 patients treated with encorafenib in combination with cetuximab only, the ORR was 46% [95% CI: 38, 53].

The safety profiles of encorafenib in combination with cetuximab and of mFOLFOX6 have been previously characterized. The safety of encorafenib in combination with cetuximab and mFOLFOX6 is consistent with the safety profile observed when each component of the combination regimen is administered separately. The safety profile of EC + mFOLFOX6 is acceptable and based on the observed ORR the BREAKWATER trial demonstrates an overall favorable benefit-risk profile. No new safety signals were identified during the review, no new Warnings and Precautions were added to the encorafenib US prescribing information, and no REMS is required for the safe and effective use of EC + mFOLFOX6 for this indication.

A PMR was issued to complete the BREAKWATER study entitled, “An Open-Label, Multicenter, Randomized Phase 3 Study of EC Alone (EC Arm) Or In Combination With Chemotherapy (mFOLFOX6; EC + mFOLFOX6 Arm) Versus Standard-of-Care Chemotherapies (Control Arm: mFOLFOX6, FOLFOXIRI, or CAPOX Each With or Without Bevacizumab) in First-Line Participants With *BRAF V600E*-Mutant mCRC” to confirm the benefit of EC + mFOLFOX6 in *BRAF V600E* mutation-positive mCRC. As of the data cutoff date (December 22, 2023) this study was completely enrolled and is expected to have the PFS read out in March 2025.

1.3. **Benefit-Risk Assessment (BRA)**

Benefit-Risk Summary and Assessment

Colorectal cancer (CRC) is estimated to be the fourth most common cancer diagnosed and the second most common cause of cancer death in the United States (US) in 2024, comprising 7.6% of all new cancer cases with an estimated 152,810 new cases of CRC and 53,010 CRC deaths (SEER 22). The 5-year relative survival rate for patients diagnosed with metastatic CRC is 15.7% and median survival has been observed to be between 2 to 3 years (SEER 22, Biller et al. 2021). Standard-of-care first-line therapy for patients with advanced or metastatic colorectal cancer includes a fluoropyrimidine-based chemotherapy regimen generally administered as a combination with leucovorin, oxaliplatin, or irinotecan. In patients who are eligible bevacizumab is added to this regimen. Treatment may also include cetuximab in patients with RAS wild-type, EGFR-expressing CRC or panitumumab in patients with wild-type RAS mCRC. These regimens have been evaluated in patients with and without *BRAF V600E* mutations and the response rates supporting their use is based on an all-comer population. The standard-of-care therapies included in the BREAKWATER trial included mFOLFOX6, FOLFOXIRI (or mFOLFIRINOX), or CAPOX each with or without bevacizumab.

BRAF mutations occur in 8-12% of patients with mCRC and are associated with a poor prognosis and shorter overall survival (Tabernero 2022). There are no FDA approved therapies indicated for the first-line treatment of patients with mCRC with *BRAF V600E* mutations. Encorafenib in combination with cetuximab was approved in 2020 for the treatment of adult patients with mCRC with *BRAF V600E* mutations based on data from the BEACON trial demonstrating an improvement in overall survival (OS) with encorafenib and cetuximab (8.4 months [95% CI: 7.5, 11.0]) compared to the control arm (5.4 months [95% CI: 4.8, 6.6]). Patients in this trial were required to have disease progression after one or two prior regimens.

The Applicant submitted data from the BREAKWATER trial to support accelerated approval of encorafenib in combination with cetuximab and mFOLFOX6 (EC + mFOLFOX6) for the treatment of adult patients with metastatic CRC with a *BRAF V600E* mutation. The BREAKWATER trial is a randomized, active-controlled, open-label study designed to compare the efficacy of EC + mFOLFOX to standard-of-care chemotherapy, which included mFOLFOX6, FOLFOXIRI, or CAPOX each with or without bevacizumab (Control Arm). The primary efficacy population included the first 220 patients randomized 1:1 to the EC + mFOLFOX6 Arm or the Control Arm. The ORR per RECIST v1.1 as assessed by BICR was 61% [95% CI: 51.6, 69.5] for the EC + mFOLFOX6 Arm and 40% [95% CI: 31.3, 49.3] for the Control Arm. The median DOR was 13.9 months [95% CI: 8.5, NE] and 11.1 months [95% CI: 6.7, 12.7], respectively. BREAKWATER was initially designed as a three-arm trial, that included a treatment arm of encorafenib in combination with cetuximab (EC Arm). The EC Arm was discontinued prior to the ORR analysis based on preliminary data from the safety lead-in portion of the study. Supportive data from the ORR analysis of the EC Arm demonstrated an

ORR of 46% [95% CI: 38, 53], which is substantially lower than the ORR observed with encorafenib in combination with cetuximab and mFOLFOX6, demonstrating the need for all components of the EC + mFOLFOX6 regimen.

The data submitted to support the safety review of EC + mFOLFOX6 is adequate to characterize the toxicity in patients with mCRC with a *BRAF V600E* mutation. The safety profile observed in patients who received encorafenib in combination with cetuximab and mFOLFOX6 is generally consistent with what has been observed in patients treated with encorafenib and cetuximab in combination and with mFOLFOX6.

Risk minimization strategies have been instituted via management guidelines in the US Prescribing Information (USPI) and the Medication Guide. Significant adverse events associated with encorafenib in combination with cetuximab and mFOLFOX6 include new primary malignancies, hepatotoxicity, hemorrhage, QT prolongation and these safety concerns were adequately addressed in the Warnings and Precautions and dose modification guidelines in the USPI.

The data submitted meets the statutory evidentiary requirement for accelerated approval and provides preliminary evidence of the effectiveness of encorafenib in combination with cetuximab and mFOLFOX6 for the treatment of adult patients with mCRC with BRAF V600E mutation. The review team recommends granting accelerated approval. A PMR for fully enrolled confirmatory study BREAKWATER CRC will be issued with the approval of this supplemental NDA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Colorectal cancer accounts for 7.6% of all new cancer cases • It is estimated that there will be 152,810 new cases of colorectal cancer and 53,010 colorectal cancer deaths in 2024 (SEER 22) • The 5-year relative survival rate of metastatic colorectal cancer is 15.7%. • New cases of colorectal cancer are diagnosed at a higher rate in patients from historically underrepresented racial groups, with the average rate of new colorectal cancer cases observed to be 43.3 in American Indian and Alaskan Natives, 40.3 in Blacks, 36 in Whites, and 28.7 in Asian and Pacific Islanders per 100,000 and at a rate of 33 per 100,000 in Hispanic/Latino individuals (U.S. Cancer Statistics Working Group 1999-2021).	Colorectal cancer is a serious and life-threatening condition with a poor prognosis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Standard-of-care first-line therapy for mCRC includes treatment with a fluoropyrimidine-, oxaliplatin-, and irinotecan-based therapy with or without bevacizumab or treatment with cetuximab (in patients with KRAS wild-type, EGFR-expressing CRC) or panitumumab (in patients with wild-type RAS mCRC).	First-line options for the treatment of patients with mCRC includes fluoropyrimidine-, oxaliplatin-, and irinotecan-based therapy with or without bevacizumab or treatment with cetuximab or panitumumab. Response rates with these therapies have ranged from 33% to 60% in patients with CRC, regardless of *BRAF V600E* status. There are no targeted therapies that are FDA-approved for the first-line treatment of patient with mCRC with a *BRAF V600E* mutation.
Benefit	• In the BREAKWATER trial, EC + mFOLFOX6 demonstrated a statistically significant and clinically meaningful improvement in BICR-ORR compared to SOC chemotherapy (61% [95% CI: 51.6, 69.5] versus 40% [95% CI: 31.3, 49.3], respectively) • The ORR of EC + mFOLFOX6 was numerically higher than the ORR observed in patients treated with encorafenib and cetuximab alone (46% [95% CI: 38, 53]), demonstrating the necessity of EC and mFOLFOX6 for the treatment effect observed with the combination regimen. • A PMR will be issued to complete and submit the PFS results from the fully enrolled BREAKWATER trial entitled, "An Open-Label, Multicenter, Randomized Phase 3 Study of EC Alone (EC Arm) Or In Combination With Chemotherapy (mFOLFOX6; EC + mFOLFOX6	The study demonstrated a clinically meaningful and statistically significant ORR accompanied by a clinically meaningful duration of response in patients with *BRAF V600E* mutation-positive mCRC. Results of the PFS and OS analysis from the BREAKWATER trial will be submitted as a PMR to confirm the benefit of EC + mFOLFOX6.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Arm) Versus Standard-of-Care Chemotherapies (Control Arm: mFOLFOX6, FOLFOXIRI, or CAPOX Each With or Without Bevacizumab) in First-Line Participants With BRAF V600E-Mutant mCRC."	
Risk and Risk Management	• The safety analysis population included the first 110 patients enrolled to each arm in the BREAKWATER trial. • The most common adverse reactions (≥25%) adverse reactions of encorafenib when used in combination with cetuximab and mFOLFOX6 were peripheral neuropathy, nausea, fatigue, anemia, rash, diarrhea, decreased appetite, vomiting, hemorrhage, abdominal pain, and pyrexia. • The most common Grade 3 or 4 laboratory abnormalities (≥10%) of encorafenib when used in combination with cetuximab and mFOLFOX6 were increased lipase, decreased neutrophil count, decreased hemoglobin, decreased white blood cell count, and increased glucose. • Serious adverse reactions occurred in 38% of patients. Fatal gastrointestinal perforation occurred in 0.9% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6.	The safety of encorafenib in combination with cetuximab and mFOLFOX6 has been well characterized in the BREAKWATER trial and in prior studies of the separate components identified during this review. No new Warnings & Precautions were identified and no REMS will be required. The observed adverse reactions were manageable with dose modifications. The risks associated with this regimen are considered acceptable in the context of the clinical efficacy in a metastatic CRC population with BRAF V600E mutation. No new safety concerns were identified.

1.4. **Patient Experience Data**

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

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	☐ Clinical outcome assessment (COA) data, such as	[eg, Section 6.1 Study endpoints]

			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (eg, individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[eg, Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (eg, submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X _____

Jamie Brewer, MD
Cross-Disciplinary Team Leader

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2. Therapeutic Context

2.1. **Analysis of Condition**

The Applicant's Position:

Metastatic CRC continues to be a life-threatening condition. Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, with more than 1.9 million new CRC cases (including anus) and 935,000 deaths estimated in 2020 according to the WHO (Sung et al, 2021). In the US, CRC is the third leading cause of cancer-related deaths in men and in women, and the second most common cause of cancer deaths when numbers for men and women are combined (American Cancer Society, 2022). The estimated number of new CRC cases for 2023 is 153,020 resulting in an estimated 52,550 deaths in the US (National Cancer Institute, 2023). Approximately 25% of patients present with metastases and 50% of patients eventually develop metastatic disease (Van Cutsem et al, 2014).

BRAF V600E mutations occur in approximately 8% to 12% of patients with mCRC and confer a poor prognosis (Tabernero et al, 2022a). *BRAF* V600 mutations lead to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signaling, resulting in increased cell proliferation and survival (Corcoran et al, 2012). This disease remains a high unmet medical need.

Nonclinical studies in *BRAF*-mutant mCRC cell lines have shown that BRAF inhibition induces a rapid feedback activation of EGFR that supports continued proliferation of *BRAF* V600E-mutant tumor cells. These effects can be overcome with concomitant inhibition of BRAF and EGFR (Corcoran et al, 2012; Prahallad et al, 2012). Additionally, results of nonclinical in vivo studies of EC combined with chemotherapy regimens support the combination of cytotoxic chemotherapy and molecular-targeted therapy as a promising therapeutic approach in the first-line treatment of *BRAF* V600E-mutant mCRC (Napolitano et al, 2023).

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

The incidence of new cases of colorectal cancer per 100,000 is highest in American Indian and Alaskan Natives (43.3), followed by Non-Hispanic Blacks (40.3), Whites (36), and Asian and Pacific Islanders (28.7). The rate of new incident cases of colorectal cancer in Hispanic/Latino individuals is 33 per 100,000 (U.S. Cancer Statistics Working Group 1999-2021). There is insufficient data regarding the distribution of *BRAF V600E* mutations among different racial and ethnic groups with mCRC.

2.2. **Analysis of Current Treatment Options**

Specific treatments for patients with *BRAF* V600E-mutant mCRC are limited. The EC combination was approved in 2020 for the treatment of patients with *BRAF* V600E-mutant mCRC after prior therapy on the basis of results from the BEACON study (Kopetz et al, 2019).

However, currently no treatments are indicated specifically for patients with *BRAF* V600E-mutant mCRC in the first-line setting and thus these patients receive systemic therapy that is recommended for mCRC in general. The common regimens used in patients with mCRC include mFOLFOX6, FOLFIRI, FOLFOXIRI, and CAPOX each with or without bevacizumab (Cervantes et al, 2023; NCCN, 2024).

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
First-Line Treatment of mCRC				
Unselected Patients, Chemotherapy and anti-VEGF				
Camptosar (irinotecan)[a] 2000 Full approval	First-line therapy in combination with 5-FU and LV for patients with metastatic carcinoma of the colon or rectum	*Design* Two Phase 3 multinational, randomized, controlled trials Study 1: compared combination irinotecan/bolus 5-FU/LV therapy given QW with a standard bolus regimen of 5-FU/LV alone given daily for 5 d Q4W; an irinotecan-alone treatment arm given on a QW schedule was also included Study 2: evaluated 2 different methods of administering infusional 5-FU/LV, with or without irinotecan *Dose* **Regimen 1:** 125 mg/m^2 IV infusion over 90 min on d 1,8,15,22 with LV 20 mg/m^2 IV bolus infusion on d 1,8,15,22 followed by 5-FU IV bolus infusion on d 1, 8, 15, 22 Q6W **Regimen 2:** 180 mg/m^2 IV infusion over 90 min on d 1, 15, 29 with LV 200 mg/m^2 IV infusion over 2 h on d 1, 2, 15, 16, 29, 30 followed by 5-FU 400 mg/m^2 IV bolus infusion on d 1, 2, 15, 16, 29, 30 and 5-FU 600 mg/m^2 IV infusion over 22 h on d 1, 2, 15, 16, 29, 30	Study 1: Primary EP OS: 14.8 mo vs 12 mo ORR: 39% vs 18% mTTP: 7 mo vs 4.2 mo Study 2: Primary EP OS: 17.4 mo vs 14.1 mo ORR: 35% vs 22% mTPP: 6.7 mo vs 4.4 mo	• Diarrhea and cholinergic reactions • Myelosuppression • Increased risk for neutropenia in patients with reduced UGT1A1 activity • Hypersensitivity • Renal Impairment / renal failure • Pulmonary toxicity • Toxicity of the 5-Day regimen • Embryo-fetal toxicity • Patients with hepatic impairment

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
Xeloda (capecitabine)[b] 2001 Full approval	First-line as monotherapy when treatment with fluoropyrimidine therapy alone is preferred A survival benefit over 5-FU/LV has not been demonstrated with monotherapy. Use instead of 5-FU/LV in combinations has not been adequately studied to assure safety or preservation of the survival advantage	*Design* Two identical open-label, multicenter, randomized, controlled clinical trials with capecitabine vs 5-FU/LV *Dose* 1250 mg/m^2 BID orally for 2 wk followed by a 1-wk rest period in 3-wk cycles	*Studies 1&2: capecitabine vs 5-FU/LV:* OS not statistically significant (a non-inferiority study design) ORR: 21% vs 11%, 21% vs 14%	• Coagulopathy • Diarrhea • Cardiotoxicity • Increased risk of severe or fatal adverse reactions in patients with low or absent dihydropyrimidine dehydrogenase activity • Dehydration and renal failure • Embryo-fetal toxicity • Mucocutaneous and dermatologic toxicity • Hyperbilirubinemia • Hematologic toxicity
Eloxatin (oxaliplatin)[c] 2005 Full approval	Used in combination with infusional 5-FU/LV, is indicated for the treatment of advanced carcinoma of the colon or rectum	*Design* Multicenter, open-label, randomized controlled study of Eloxatin in combination with infusional 5-FU/LV and a combination of Eloxatin plus irinotecan with a control regimen of irinotecan plus 5-FU/LV *Dose* **Day 1**: Eloxatin 85 mg/m^2 IV infusion in 250-500 mL D5W and LV 200 mg/m^2 IV infusion in D5W both given over 120 min at the same time in separate bags using a	Primary EP OS: 19.4 mo vs 14.6 mo, HR 0.65 (0.53-0.80) ORR: 45.2% vs 32.5% mTPP: 8.7 mo vs 6.9 mo	• Hypersensitivity and anaphylactic reactions • Pregnancy Category D • Neuropathy • Neurotoxicity • Pulmonary toxicity • Hepatoxicity

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
		Y-line, followed by 5-FU 400 mg/m^2 IV bolus given over 2-4 min, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL D5W (recommended) as a 22-h continuous infusion **Day 2**: LV 200 mg/m^2 IV infusion over 120 min, followed by 5-FU 400 mg/m^2 IV bolus given over 2-4 min, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL D5W (recommended) as a 22-h continuous infusion		
Avastin (bevacizumab)[d] 2004 Full approval	In combination with IV fluorouracil-based chemotherapy for first- or second-line treatment	*Design* Double blind, active controlled 1:1:1 placebo with bolus IFL, Avastin with bolus IFL or Avastin with FU/LV (Study AVF2107g) *Dose* • 5mg/kg IV Q2W in combination with bolus IFL • 10 mg/kg IV Q2W in combination with FOLFOX4 • 5 mg/kg IV Q2W or 7.5 mg/kg IV Q3W in combination with fluoropyrimidine-irinotecan-or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a 1L Avastin-containing regimen	Primary EP OS: 20.3 mo vs 15.6 mo, HR 0.66 PFS: 10.6 mo vs 6.2 mo, HR 0.54 ORR: 45% vs 35% DOR: 10.4 mo vs 7.1 mo	• Gastrointestinal perforations and fistula • Surgery and wound healing complications • Hemorrhage • Arterial thromboembolic events • Venous thromboembolic events • Hypertension • Posterior reversible encephalopathy syndrome • Renal injury and proteinuria • Infusion-related reactions • Embryo-fetal toxicity • Ovarian failure • Congestive heart failure

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
RAS WT, EGFR Antagonists				
Erbitux (cetuximab)[e] 2012 Full approval	Treatment of *KRAS* wild-type*, EGFR-expressing, mCRC as determined by an FDA-approved test in combination with FOLFIRI for first-line treatment *Initial indications for cetuximab were for unselected patients, labels were restricted to *KRAS* WT patients in 2009 based on retrospective data analyses	*Design* Open label, randomized 1:1 to receive Cetuximab+FOLFIRI vs FOLFIRI in EGFR-expressing mCRC patients *Dose* Weekly Dosage • Initial dose: 400 mg/m^2 as a 120-min IV infusion • Subsequent doses: 250 mg/m^2 as 60-min IV infusion QW Biweekly Dosage • Initial and subsequent doses: 500 mg/m^2 administered as a 120-min IV Q2W • Complete Erbitux administration 1 h prior to irinotecan or FOLFIRI	PFS: 9.5 mo vs 8.1 mo, HR 0.7 OS: 23.5 mo vs 19.5 mo, HR 0.8 ORR: 57% vs 39%	• Infusion reactions • Cardiopulmonary arrest • Pulmonary toxicity • Dermatologic toxicity • Hypomagnesemia and accompanying electrolyte abnormalities • Increased tumor progression, increased mortality, or lack of benefit in patients with *RAS*-mutant mCRC • Embryo-fetal toxicity
Vectibix (panitumumab)[f] 2014 Full approval	Treatment of wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) mCRC in combination with FOLFOX for first-line treatment	*Design* Multicenter, open-label, randomized (1:1) to receive Vectibix+FOLFOX vs FOLFOX in untreated mCRC *Dose* 6 mg/kg every 14 d IV over 60 or 90 min	PFS: 9.6 mo vs 8 mo, HR 0.8 ORR: 54% vs 47% OS (exploratory): 23.8 mo vs 19.4 mo	• Dermatologic and soft tissue toxicity • Increased tumor progression, increased mortality, or lack of benefit in patients with *RAS*-mutant mCRC • Electrolyte depletion/monitoring: monitor electrolytes and institute appropriate treatment • Infusion reactions • Pulmonary

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
				fibrosis/interstitial lung disease • Ocular toxicities • Embryo-fetal toxicity
MSI-H or dMMR				
Keytruda (pembrolizumab)[g] 2020 Full approval	Treatment of patients with unresectable or metastatic MSI-H or dMMR CRC	*Design* KEYNOTE-177: multicenter, randomized, open-label, active-controlled trial, 1:1 Pembrolizumab vs investigators choice chemotherapy (FOLFOX/FOLFIRI -/+ bevacizumab) *Dose* 200 mg Q3W or 400 mg Q6W	PFS: 16.5 mo vs 8.2 mo, HR 0.6 OS: NR vs 36.7 mo, HR 0.74 ORR: 44% vs 33% DOR (mo): NR (2.3+, 41.4+) vs 10.6 (2.8, 37.5+)	• Immune-mediated adverse reactions • Infusion-related reactions • Complications of allogeneic HSCT • Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials • Embryo-fetal toxicity
Second-Line Treatment of mCRC				
Unselected Patients – Cytotoxic Agents				
CAMPTOSAR (irinotecan) [a] 1996 Accelerated approval 1998 Full approval	Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based	*Design* • Studies 3, 4 and 5: open-label, single-agent studies in patients who had progressed following 5-FU-based therapy. 6-wk cycles of 90 min IV QW for 4 wk, followed by 2-wk rest • Study 6: single-arm, Q3W dosage schedule after 5-FU • Studies 7 and 8: randomized for QW dosing	*Once Weekly Dosing Studies* ORR Study 3: 21% (95% CI, 9.3 to 32.3) ORR Study 4: 13% (95% CI, 6.3 to 20.4) ORR Study 5 (125 mg/m^2/wk): 14% (95% CI, 5.5 to 22.6) ORR Study 5 (100 mg/m^2/wk):	• Diarrhea and cholinergic reactions • Myelosuppression • Neutropenia in patients with reduced UGT1A1 • Hypersensitivity • Renal impairment/renal failure • Pulmonary toxicity • Toxicity of the 5-Day

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
	therapy	• Study 7: compared irinotecan with BSC • Study 8: irinotecan vs 5-FU *Dose* *Combination* **Regimen 1**: 125 mg/m^2 IV over 90 min on d 1, 8,15, 22 with LV 20 mg/m^2 IV bolus on d 1, 8, 15, 22 followed by 5-FU IV bolus infusion on d1, 8, 15, 22 Q6W **Regimen 2**: 180 mg/m^2 IV over 90 min on d 1, 15, 29 with LV 200 mg/m^2 IV infusion over 2 h on d 1, 2, 15, 16, 29, 30 followed by 5-FU 400 mg/m^2 IV bolus infusion on d 1, 2, 15, 16, 29, 30 and 5-FU 600 mg/m^2 IV infusion over 22 h on d 1, 2, 15, 16, 29, 30 *Single Agent* **Regimen 1**: 125 mg/m^2 IV over 90 min on d 1, 8, 15, 22 then 2-wk rest **Regimen 2**: 350 mg/m^2 IV infusion over 90 min on d 1 Q3W	9% (95% CI, 3.3 to 14.3) *Once Every 3-Week Dosing Studies* ORR Study 6: 12.1% (95% CI, 7.0% to 18.1%) OS Study 7 (irinotecan vs BSC): 9.2 mo vs 6.5 mo (p=0.0001) OS Study 8 (irinotecan vs 5-FU): 10.8 mo vs 8.5 mo (p=0.035)	regimen • Embryo-fetal toxicity • Patients with hepatic impairment

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
Eloxatin (oxaliplatin)[c] 2002 Full approval	In combination with infusional 5-FU/LV for treatment of advanced CRC	*Design* Open-label, randomized, 3-arm controlled study Eloxatin + 5-FU/ LV vs 5-FU/LV vs Eloxatin *Dose* **Day 1**: Eloxatin 85 mg/m^2 IV infusion in 250-500 mL D5W and LV 200 mg/m^2 IV infusion in D5W both given over 120 min at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m^2 IV bolus given over 2-4 min, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL D5W (recommended) as a 22-h continuous infusion **Day 2**: LV 200 mg/m^2 IV infusion over 120 min, followed by 5-FU 400 mg/m^2 IV bolus given over 2-4 min, followed by 5-FU 600 mg/m^2 IV infusion in 500 mL D5W (recommended) as a 22-h continuous infusion	ORR: 9% vs 0% Median TTP: 4.6 mo vs 2.7 mo	• Hypersensitivity and anaphylactic reactions • Pregnancy Category D • Neuropathy • Neurotoxicity • Pulmonary toxicity • Hepatoxicity
Unselected Patients – Anti-angiogenic Agents				
Avastin (bevacizumab) [d] 2006 Full approval	In combination with IV fluorouracil-based chemotherapy, is indicated for the first-or second-line treatment of patients with mCRC In combination with	*Design* Study E3200: 1:1:1 Avastin + FOLFOX4 vs FOLFOX4 vs Avastin alone. Avastin alone was closed after planned IA ML18147: prospective, randomized, open-label 1:1 Avastin + fluoropyrimidine-based chemotherapy vs fluoropyrimidine-based chemotherapy *Dose*	*E3200* OS: 13 mo vs 10.8 mo, HR 0.75 *ML18147* OS: 11.2 mo vs 9.8 mo, HR 0.81 PFS: 5.7 mo vs 4.0 mo, HR 0.68	• Gastrointestinal perforations and fistula • Surgery and wound healing complications hemorrhage • Arterial thromboembolic events • Venous thromboembolic events • Hypertension • Posterior reversible

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
	fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen	• 5mg/kg IV Q2W in combination with bolus-IFL • 10 mg/kg IV Q2W in combination with FOLFOX4 • 5 mg/kg IV Q2W or 7.5 mg/kg IV Q3W in combination with fluoropyrimidine-irinotecan-or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a 1L Avastin-containing regimen		encephalopathy syndrome • Renal injury and proteinuria • Infusion-related reactions • Embryo-fetal toxicity • Ovarian failure • Congestive heart failure
Zaltrap (ziv-aflibercept)[h] 2012 Full approval	In combination with FOLFIRI, is indicated for patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen	*Design* Randomized, double-blind, placebo-controlled study 1:1 Zaltrap/FOLFIRI vs Placebo/FOLFIRI *Dose* 4 mg/kg as an IV infusion over 1 h Q2W	OS: 13.5 mo vs 12.1 mo, HR 0.82 PFS: 6.9 mo vs 4.7 mo, HR 0.76 ORR: 19.8% vs 11.1%	• Hemorrhage • Gastrointestinal perforation • Compromised wound healing • Fistula formation • Hypertension • Arterial thromboembolic events • Proteinuria • Neutropenia and neutropenic complications • Diarrhea and dehydration • Reversible posterior leukoencephalopathy syndrome • Embryo-fetal toxicity

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
Cyramza (ramucirumab)[i] 2015 Full approval	In combination with FOLFIRI, for the treatment of patients with mCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine	*Design* Randomized, double-blind study in patients with mCRC with disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. 1:1 Cyramza 8 mg/kg IV plus FOLFIRI IV Q2W or placebo plus FOLFIRI IV Q2W *Dose* 8 mg/kg Q2W administered by IV infusion over 60 min prior to FOLFIRI administration	OS: 13.3 mo vs 11.7 mo, HR 0.85 PFS: 5.7 mo vs 4.5 mo, HR 0.79	• Arterial thromboembolic events • Hypertension • Infusion-related reactions • Impaired wound healing • Clinical deterioration in patients with cirrhosis • Reversible posterior leukoencephalopathy syndrome • Proteinuria including nephrotic syndrome • Thyroid dysfunction • Embryo-fetal risk
2L+ *RAS* WT Patients				
EGFR Antagonists				
Erbitux (cetuximab)[e] 2004 Accelerated approval 2007 Full (mono) 2021 Full (combo-encorafenib)	*KRAS* wild-type*, EGFR-expressing mCRC: In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy; As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to	*Design* *Combination* BOND: multicenter trial in patients with EGFR-expressing recurrent mCRC, randomized (2:1) to receive either Erbitux in combination with irinotecan or Erbitux single agent *Single-Agent* Study CA225-025: multicenter, open-label, randomized, clinical trial with EGFR-expressing, previously treated, recurrent mCRC. Patients were randomized (1:1) to receive either Erbitux with BSC or BSC alone.	*BOND* Primary EP ORR: 23% vs 11% mDOR: 5.7 mo vs 4.2 mo mTTP: 4.1 mo vs 1.5 mo *CA225-025* Primary EP OS: 8.6 mo vs 5.0 mo, HR 0.63	• Infusion reactions • Cardiopulmonary arrest • Pulmonary toxicity • Dermatologic toxicity • Hypomagnesemia and accompanying electrolyte abnormalities • Increased tumor progression, increased mortality, or lack of benefit in patients with *RAS*-mutant mCRC • Embryo-fetal toxicity

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
	irinotecan; In combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy *Initial indications for cetuximab were for unselected patients, label were restricted to *KRAS* WT patients in 2009 based on retrospective data analyses	*Dose* Weekly Dosage • Initial dose: 400 mg/m^2 administered as a 120-min IV infusion • Subsequent doses: 250 mg/m^2 administered as a 60-min infusion QW Biweekly Dosage • Initial and subsequent doses: 500 mg/m^2 administered as a 120-minute IV infusion Q2W		
Vectibix (panitumumab) [f] 2006 Accelerated approval 2014 Full approval	As monotherapy, for the treatment of patients with wild-type *KRAS* (exon 2 in codons 12 or 13) mCRC, as determined by an FDA-approved test for this use,	*Design* • Study 20020408: randomized 1:1 Vectibix+ BSC vs BSC alone • Study 20080763: open-label, multicenter, randomized (1:1) Vectibix vs cetuximab • Study 20100007: open-label, randomized 1:1 Vectibix + BSC vs BSC, *KRAS* WT (ex-US study)	*Study 20020408* PFS: 96 d vs 60 d HR 0.45 *Study 20080763* Primary EP OS: 10.4 mo vs 10.0 mo, HR 0.97 (non-inferiority) PFS: 4.1 mo vs 4.4 mo, HR	• Dermatologic and soft tissue toxicity • Increased tumor progression, increased mortality, or lack of benefit in patients with *RAS*-mutant mCRC • Electrolyte depletion/monitoring: monitor electrolytes and

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
	following disease progression on fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens *Initially approved in unselected patients by the FDA and the label was restricted to *RAS* WT patients in 2009	*Dose* 6 mg/kg every 14 d as an IV infusion over 60 min (≤1000 mg) or 90 min (>1000 mg)	1.00 ORR: 22% vs 19% *Study 20100007* Primary EP OS: 10.0 mo vs 7.4 mo, HR 0.73 PFS: 3.6 mo vs 1.7 mo, HR 0.51 ORR: 27% vs 1.6%	institute appropriate treatment • Infusion reactions • Pulmonary fibrosis/interstitial lung disease • Ocular toxicities • Embryo-fetal toxicity
2L+ Checkpoint Inhibitors				
Keytruda (pembrolizumab)[g] 2017 Accelerated approval 2023 Full approval	Indicated for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options	*Design* KEYNOTE-164: uncontrolled, open-label, single-arm trial *Dose* 200 mg Q3W or 400 mg Q6W	*KEYNOTE-164* ORR: 34% (95% CI: 26%, 43%) DOR Range (mo): 4.4+, 58.5+	• Immune-mediated adverse reactions • Infusion-related reactions • Complications of allogeneic HSCT • Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials • Embryo-fetal toxicity

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
Opdivo (nivolumab)[j] 2017 Accelerated approval	As a single agent or in combination with ipilimumab for the treatment of adult and pediatric patients 12 years and older with MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan	*Design* CHECKMATE-142: non-randomized, multiple-parallel cohort, open label, dMMR or MSI-H, single-agent OPDIVO or OPDIVO and ipilimumab dMMR or MSI-H mCRC cohort *Dose* • Adult and pediatric patients ≥40 kg: 240 mg Q2W or 480 mg Q4W • Pediatric patients <40 kg: 3 mg/kg Q2W • Adult and pediatric patients ≥40 kg: 3 mg/kg followed by ipilimumab 1 mg/kg on the same day Q3W for 4 doses, then 240 mg Q2W or 480 mg Q4W	*Single Agent MSI-H/dMMR Cohort* ORR: 32% CR: 9% ≥6 mo DOR: 94%, ≥12 mo DOR: 88% *With Ipilimumab MSI-H/dMMR Cohort* ORR: 56% CR: 13% ≥6 mo DOR: 87%, ≥12 mo DOR: 74%	• Immune-mediated adverse reactions • Infusion-related reactions • Complications of allogeneic HSCT • Embryo-fetal toxicity
Yervoy (ipilimumab)[k] 2018 Accelerated approval	In combination with nivolumab for the treatment of adult and pediatric patients 12 years of age and older with MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan	*Design* CHECKMATE-142: non-randomized, multiple-parallel cohort, open label, Opdivo and ipilimumab dMMR or MSI-H mCRC cohort *Dose* 1 mg/kg Q3W with nivolumab 3 mg/kg (30-min IV infusion on the same day)	*CHECKMATE-142* ORR: 56% CR: 13% ≥6 mo DOR: 87%, ≥12 mo DOR: 74%	• Severe and fatal immune-mediated adverse reactions • Infusion-related reactions • Complications of allogeneic HSCT • Embryo-fetal toxicity

Table 1. Applicant - Summary of FDA-Approved Treatments Relevant to the Proposed Indication

Product Name/Year and Approval Scope	Indication	Pivotal Trial Design/Dose	Efficacy Information	Warnings and Precautions
2L+ BRAF Inhibitor				
Braftovi (encorafenib)[1] 2019 Full approval	In combination with cetuximab, for the treatment of adult patients with mCRC with a *BRAF* V600E mutation, as detected by an FDA-approved test, after prior therapy	*Design* BEACON: randomized, active-controlled, open-label, multicenter trial, 1:1:1 Braftovi + cetuximab vs Braftovi + binimetinib+ cetuximab vs FOLFIRI + cetuximab or irinotecan + cetuximab *Dose* 300 mg orally QD in combination with cetuximab	*BEACON* OS: 8.4 mo vs 5.4 mo, HR 0.6 ORR: 20% vs 2% PFS: 4.2 mo vs 1.5 mo, HR 0.4	• New primary malignancies, cutaneous and non-cutaneous • Tumor promotion in *BRAF* wild-type tumors • Hemorrhage • Uveitis • QT prolongation • Embryo-fetal toxicity

a. (CAMPTOSAR [irinotecan hydrochloride], 2022)
b. (XELODA [capecitabine], 2022)
c. (ELOXATIN [oxaliplatin], 2020)
d. (AVASTIN [bevacizumab], 2022)
e. (ERBITUX [cetuximab], 2021)
f. (VECTIBIX [panitumumab], 2021)
g. (KEYTRUDA [pembrolizumab], 2023)
h. (ZALTRAP [ziv-aflibercept], 2020)
i. (CYRAMZA [ramucirumab], 2022)
j. (OPDIVO [nivolumab], 2023)
k. (YERVOY [ipilimumab], 2023)
l. (BRAFTOVI [encorafenib] USPI, 2023)

The Applicant's Position:
BRAF V600E-mutant mCRC remains an aggressive disease that has a poor prognosis and there remains a need to develop new treatment regimens to expand the therapeutic options for patients. Treatment with the combination of EC + mFOLFOX6 may offer a new standard of care for patients with *BRAF V600E*-mutant mCRC.

The FDA's Assessment:
FDA generally agrees with the Applicant's description of the current treatment landscape. There is no FDA-approved targeted therapy for the first-line treatment of patients with mCRC with a *BRAF V600E* mutation.

In the US, triplet therapy with mFOLFIRINOX is used to treat select high risk, fit patients with mCRC; however, most data to support triplet chemotherapy comes from clinical trials that have assessed FOLFOXIRI rather than FOLFIRINOX (each with or without bevacizumab). Trials have had mixed results; however, multiple trials have reported improved outcomes on one or more endpoints compared to FOLFIRI or FOLFOX (e.g., Gruppo Oncologico, 2007; TRIBE; TRIBE2; STEAM; VISNU-1; VOLFI). In general, patients with BRAF positive tumors represented small subsets of the above trials. Although FOLFOXIRI may improve outcomes (and appears to have a higher response rate than double therapy), it is associated with a higher risk of severe GI toxicity, asthenia, and neurotoxicity. Therefore, first line triplet therapy is generally limited to very fit patients and doublet therapy (generally with a biologic) remains a standard regimen for many patients with mCRC.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Marketing approvals for encorafenib have been obtained in the US as follows:

- Approved on 27 June 2018 for use in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or *BRAF* V600K mutation (NDA 210496).
- Approved on 08 April 2020 for use in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer with a *BRAF* V600E mutation, as detected by an FDA-approved test, after prior therapy (NDA 210496/S-006, Sequence 0225).
- Approved on 11 October 2023 for use in combination with binimetinib, for the treatment of adult patients with metastatic NSCLC with a *BRAF* V600E mutation, as detected by an FDA-approved test (NDA 210496/S-014, Sequence 0657).

The FDA's Assessment:

FDA agrees with the Applicant's position.

3.2. **Summary of Presubmission/Submission Regulatory Activity**

The Applicant's Position:

Table 2. Applicant - Submission Regulatory Activity

Submission/ Correspondence Date	Submission/ Correspondence	Description
12 June 2020	Type B Meeting	Type B meeting to discuss the BREAKWATER study design with FDA agreement on the following: • Sponsor proposals regarding the patient population, dosing regimen of cetuximab, planned SLI, and primary endpoint of PFS by BICR; • A CDx for MSI-H/dMMR will not be required to identify these patients; • A supplemental PMA will not be required assuming the approved CDx test, the QIAGEN *therascreen BRAF V600E* RGQ PCR Kit, has not changed.
27 July 2020	New Protocol	Following a favorable Type B meeting discussion, a new original protocol (dated 15 July 2020) was submitted in SN 1126 and the SLI portion of the study was initiated on 21 December 2020.
30 August 2022	Preliminary BTDR Meeting	Based on compelling preliminary results from the SLI portion, a Preliminary BTDR was submitted to the IND in SN 1167 on 25 July 2022. During the BTDR teleconference, the FDA acknowledged that the results from the SLI looked promising but given the small number of patients and immaturity of the data with the cutoff, coupled with the availability of encorafenib, cetuximab, and chemotherapy for mCRC patients, the FDA believed it was premature for the Sponsor to submit a full BTD at that time. FDA suggested that submission of the full BTD application at the time of the sNDA would have the benefit of an increased likelihood for an expedited review.
07 November 2022	Type C Meeting	The following key agreements were reached during the meeting: • Addition of ORR as a primary endpoint in the Phase 3 portion of the BREAKWATER study and conducting the ORR analyses at the time the Phase 3 portion of the study is fully enrolled or 8 months after randomization of the first 110 participants in each arm (whichever occurs later), to support AA of the EC + mFOLFOX6 combination in first-line patients, with conversion to FA based on the final PFS analysis from the same study; acceptance of the revised statistical testing strategy for the study;

Table 2. Applicant - Submission Regulatory Activity

Submission/ Correspondence Date	Submission/ Correspondence	Description
		• Discontinuation of enrollment of Arm A (EC Arm); • Addition of a randomized cohort of first-line EC + FOLFIRI vs FOLFIRI (with or without bevacizumab) to support a potential AA based on ORR with conversion to FA based on robust PFS from the same cohort. In addition, FDA agreed to the potential for BREAKWATER to support (b) (4) indication.
23 December 2022	Protocol Amendment 5 (dated 20 December 2022)	BREAKWATER protocol was amended to incorporate agreements from the Type C meeting.
03 May 2023	Type C Format and Content Meeting	Key agreements reached regarding the format and content of the 4 sNDAs for AA and FA for both chemotherapy regimens: • Agreement on the overall proposed format and content of the sNDAs, FDA stated that in order to go forward with the current strategy of sequential approval of 2 chemotherapy backbones it will be critical to ensure that the submission of EC + FOLFIRI is prior to full approval of EC + mFOLFOX6, since EC + mFOLFOX6 will be considered as available therapy after full approval against which EC + FOLFIRI will be compared against. • Further justification on the ADR selection strategy. • Submission of a Diversity Plan as soon as possible. • Agreement on the pooling strategy for limited safety analyses in which safety data for the EC + mFOLFOX6 Cohort of the SLI will be pooled with the corresponding EC + mFOLFOX6 Arm of Phase 3 and presented side-by-side and as a pooled population for AESIs and ADRs only.
22 June 2023	Initial Diversity Plan	An initial Diversity Plan for the BREAKWATER study for enrollment of underrepresented racial and ethnic participants study was submitted.
28 June 2023	Submitted Agreed iPSP	A request for Full Waiver of Pediatric Studies for encorafenib in combination with cetuximab and mFOLFOX6 or FOLFIRI for the treatment of patients with CRC with a *BRAF V600E* mutation was conditionally agreed to with the FDA in the Written Response to the Initial Pediatric Study Plan, received on 13 June 2023. The Agreed iPSP was subsequently submitted to the IND and Agreement received on 27 July 2023.

Table 2. Applicant - Submission Regulatory Activity

Submission/ Correspondence Date	Submission/ Correspondence	Description
05 July 2023	Type D WRO	A request for clarification of the 03 May 2023 Type C Format and Content Meeting was converted to a Type D meeting WRO where the Agency agreed on: • The approach for selection of ADRs with BEACON ADRs as the starting point and identification of new potential ADRs that are uniquely and likely associated with the combination regimen (encorafenib + cetuximab + chemotherapy) specific to BREAKWATER. The final decision will be made based on FDA review of the adverse event dataset. • Strategy, format and content for the ISE and ISS (BREAKWATER and BEACON data in a side-by-side format). • Clarification that LHY746 is not an active metabolite of encorafenib.
08 March 2024	SAP Version 6 (dated 08 March 2024)	Updated the required number of PFS events for the final analysis and as a result, decreased the power for the sample size calculation for PFS of Phase 3 portion prior to the Phase 3 ORR analysis database snapshot.
15 March 2024	Protocol Amendment 6 (dated 13 March 2024)	Amended as per SAP Version 6 to modify the required number of PFS events by BICR needed to conduct the primary PFS analysis for the Phase 3 portion of the study to enable a timely readout of the PFS given a slower-than-expected accrual of events. In addition, updates were made to comply with EU CTR content requirements, Sponsor template requirements, and to modify the analyses of cfDNA to incorporate recent findings from ctMoniTR project.
10 April 2024	Request for participation in RTOR	Based on the BREAKWATER study design and results meeting the eligibility criteria for RTOR, a request for participation in RTOR was submitted to the IND. Timing and components of the early and final submission package were provided along with the top-line report. FDA agreed to submitting the application under RTOR in an email communication of 15 May 2024.
12 April 2024	Request for preliminary BTDR	Based on compelling clinical results from the Phase 3 ORR PCD analyses demonstrating meaningful clinical benefit in the EC+mFOLFOX6 Arm relative to standard-of-care regimens, a request for a preliminary BTDR was submitted to the IND. This request was formally withdrawn on 30 April 2024 following a discussion with the Agency on 22 April 2024, where although FDA recognized the strength

Table 2. Applicant - Submission Regulatory Activity

Submission/ Correspondence Date	Submission/ Correspondence	Description
		of the data, the Agency stated that BTD this close to the planned submission would not expedite the review timeline and might potentially impact the integrity of the PFS analysis due to potential informative censoring.
05 June 2024 (preliminary comments received on 30 May 2024)	pre-sNDA Type B Meeting	FDA agreement received on the following: • Adequacy of the top-level clinical results from the study to support Accelerated Approval of the proposed indication. • Participation in Project Orbis. • No requirement for a supplemental PMA submission for the *BRAF V600E* test.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of regulatory interactions. Additional details of some regulatory interactions are included below:

- November 7, 2022, Type C Meeting: The Applicant informed the FDA of the plan to discontinue enrollment to Arm A (EC Arm) of the study. This decision was informed by preliminary activity observed in the safety-lead in portion of the BREAKWATER study. Based on this preliminary data, the Applicant thought the likelihood of demonstrating superiority of EC to SOC chemotherapy would be low. This conclusion was also supported by data from the ANCHOR-CRC study which showed comparable efficacy when EC in combination with binimetinib was compared to historical chemotherapy.

- April 24, 2024, Information Request: In response to the submission of SAP Version 6 (March 8, 2024) and Protocol Amendment 6 (March 13, 2024), FDA sent an information request on April 24, 2024, to enquire about the current accumulation status of PFS events and the projected date to accumulate the original target number of PFS events. In addition, FDA requested confirmation that the reduction in the total number of PFS events was not in response to efficacy in the BREAKWATER study. The Applicant clarified that the trend of slower PFS events accumulation was observed prior to the ORR analysis and confirmed that the reduction in target PFS events was made prior to the ORR analysis.

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 3 consulted OSI to discuss an audit of overall trial conduct for the BREAKWATER study. Two clinical investigators were selected for audit, Drs. Marial Elena Elez (Site 1033) and Eduardo Polo Marques (Site 1036). The Contract Research Organization (CRO), (b) (4) was chosen for inspection of the conduct of the central imaging review.

As of the data cutoff (December 22, 2023), Site 1033 screened a total of 42 patients (combined SLI and Phase 3), and 23 patients were enrolled and randomized into the Phase 3 portion of the study. A total of 18 patients were randomized in the Phase 3 EC + mFOLFOX6 and SOC arms, of which 10 patients were in the BICR-ORR primary efficacy population. The inspection reviewed patient-related source documents for the 23 randomized Phase 3 patients, including but not limited to the following: informed consent forms, medical histories, patient assessments, vital signs, physical examinations, concomitant medications, adverse events (AEs), investigational product usage, and progress notes. Inform consents documents were reviewed for 29 screened Phase 3 patients.

The inspection reviewed the following study-related documents: informed consents, protocols, curriculum vita (CV), Independent Ethics Committee (IEC) submissions and correspondence, financial disclosure statements, training records, Delegation of Authority log, Enrollment Log, Regulatory Binders, adverse event reporting, study test article accountability, records retention, monitoring reports, and the monitoring site visit log. The inspection verified that tumor assessments for the interim primary efficacy endpoint (ORR) were performed at protocol specified time points and submitted to the central imaging CRO. There was no apparent evidence of underreporting of AEs or protocol deviations. Based on the results of the inspection, study data generated at Dr. Elez's site appear acceptable in support of the proposed indication in the sNDA.

As of the data cutoff (December 22, 2023), Site 1036 screened 16 patients, and 15 patients were enrolled and randomized. A total of 13 patients were randomized in the Phase 3 EC + mFOLFOX6 and SOC arms, of which 7 patients were in the BICR-ORR primary efficacy population. The inspection reviewed patient-related source documents for the 13 patients randomized in the EC + mFOLFOX6 and SOC arms, including but not limited to the following: medical histories, subject assessments, vital signs, physical examinations, concomitant medications, AEs, investigational product usage, and progress notes. Informed-consent documents were reviewed for all 16 screened patients.

The inspection reviewed the following study-related documents: informed consents, protocols, CV, IEC submissions and correspondence, financial disclosure statements, training records, Delegation of Authority log, Enrollment Log, Regulatory Binders, adverse event reporting, study test article accountability, monitoring reports, and the monitoring site visit log. The inspection verified that tumor assessments for the interim primary efficacy endpoint (ORR) were performed at specified time points and submitted to the central imaging CRO. The inspection noted that the

screening / baseline imaging for Subjects (b) (6) were obtained prior to enrollment as part of SOC and at a different facility than used for subsequent imaging. Although the use of different imaging facilities for screening/baseline images and on-treatment images has the potential to introduce some variability in tumor measurements, the timing and magnitude of change in tumor measurements suggests it unlikely that this had an effect on the analysis of the primary endpoint.

There was no apparent evidence of underreporting of AEs and protocol deviations. The inspection identified minor GCP violations for late reporting of the following two SAEs, however this late reporting is unlikely to have had a impact on patient safety, eligibility or overall safety evaluation.

- Subject (b) (6) (SOC arm), treatment emergent Grade 2 non-neutropenic ileitis on Study Day 23, reported 6 months late.
- Subject (b) (6) (SOC arm), non-treatment emergent Grade 3 intestinal sub-occlusion on Study Day -3, reported 6 weeks late.

Based on the results of the inspection, study data generated at Dr. Marques's site appear acceptable in support of the proposed indication in the sNDA.

This inspection reviewed (b) (4) contracted responsibilities as the CRO providing BICR for BREAKWATER (Study C4221015) and included a study specific data audit. Records reviewed included Organizational Charts, business history, contracts, training and qualification records, electronic case report forms, secondary review procedures for oversight of reviewer performance and quality monitoring, and imaging source data. (b) (4) (b) (4) blinding procedures and adherence to the Independent Review Charter, including global and timepoint radiology review, were also reviewed, and found to be adequate.

The inspection verified the interim primary efficacy endpoint (ORR) for a sampling of 34 subjects enrolled in the EC + mFOLFOX6 (early responders) and SOC arms (early progressors) by comparison of source records containing the tumor measurements and response assessments with the Tumor Identification, Tumor Response, and Response Assessment data line listings. There were no discrepancies identified. Based on the results of the inspection, the imaging review data generated (b) (4) appear acceptable in support of the proposed indication in the sNDA.

4.2. **Product Quality**

No new information is provided in the current submission.

4.3. **Clinical Microbiology**

No new information is provided in the current submission.

4.4. **Devices and Companion Diagnostic Issues**

No new information is provided in the current submission.

5. Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

This submission did not require nonclinical pharmacology/toxicology review.

X X

Primary Reviewer Supervisor

6. Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:
The proposed dosing regimen of BRAFTOVI is 300 mg (same as recommended dose in combination with cetuximab for the previously approved indication for patients with metastatic CRC with a *BRAF V600E* mutation) orally once daily in combination with cetuximab and mFOLFOX6. The Applicant's proposed encorafenib dosage in combination with cetuximab and mFOLFOX6 is supported by observed efficacy and safety data in BREAKWATER as well as by the following clinical pharmacology information:

- Exposure-response (E-R) analyses indicate that there are no evident E-R relationships between exposure and efficacy in BREAKWATER.
- E-R results for safety are consistent with previous E-R analyses conducted in patients with melanoma and mCRC, which indicate a positive relationship between encorafenib exposure and Grade ≥3 adverse reactions; however, the overall toxicity profile appears tolerable and the current labeling for BRAFTOVI includes dosage modifications for the management of Grade ≥3 adverse reactions. Furthermore, no relationship was observed between encorafenib exposure and all-grade AESIs (myelosuppression, cutaneous non-squamous cell carcinoma, facial paresis, hepatic failure, QT prolongation).
- No drug-drug interactions (DDI) between encorafenib and oxaliplatin leading to altered exposure of either agent was expected or observed in BREAKWATER.

A discussion of the efficacy of encorafenib in combination with cetuximab and mFOLFOX6 is in Section 8.1.

The updated final population PK model indicates that existing dosage modification recommendations for intrinsic factors per the current USPI for BRAFTOVI remain applicable.

6.1.1. **Recommendations**

The Office of Clinical Pharmacology has reviewed the information contained in Supplement 17 of NDA 210496 and concluded that this efficacy supplement is approvable from a clinical pharmacology perspective. The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA recommended revisions to the labeling.

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The pivotal trial provided evidence of effectiveness of BRAFTOVI in combination with cetuximab and mFOLFOX6 for the proposed indication of treatment of patients with mCRC with a *BRAF V600E* mutation based on objective response rate (ORR). Overall the safety profile is consistent with the known safety profile of encorafenib and the safety profiles associated with the other components of the combination regimen. The exposure-response (E-R) analysis indicated no relationship between encorafenib exposure and the efficacy endpoint ORR in patients with mCRC. The E-R safety analysis indicated an association between encorafenib exposures and the probability of grade ≥3 TEAEs.
General dosing instructions	The recommended dosing regimen is 300 mg of BRAFTOVI in combination with cetuximab (500 mg/m^2 once every 2 weeks [Q2W]) and mFOLFOX6. BRAFTOVI may be taken with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Existing dosage modification recommendations for intrinsic factors (i.e., age, body weight, sex, mild hepatic impairment, mild or moderate renal impairment) per the current USPI for BRAFTOVI remain applicable. Results of updated population PK analysis are consistent with previously conducted analysis with no clinically significant differences in the PK of encorafenib based on age, body weight, sex, mild hepatic impairment, or eGFR (44 – 2040 mL/min).

6.1.2. **Postmarketing Requirements and Commitments**

None.

6.2. **Summary of Clinical Pharmacology Assessment**

6.2.1. **Pharmacology and Clinical Pharmacokinetics**

Data:

Reference is made to the clinical pharmacology information provided in the initial NDA 210496, the subsequent NDA 210496/S-006, Sequence 0225, and the subsequent NDA 210496/S-013, Sequence 0503.

Additional clinical pharmacology results for encorafenib that are part of this submission (sNDA) include:

- PK parameters from non-compartmental analysis of encorafenib and its (inactive) metabolite LHY746 and oxaliplatin (measured as total platinum in plasma, and platinum in plasma ultrafiltrate) from BREAKWATER participants who provided serial PK sampling.
- Results from the population PK analysis conducted using data from the BREAKWATER study will be provided in the final submission package.
- Results from the encorafenib ER analyses for selected efficacy and safety endpoints from the BREAKWATER study will be provided in the final submission package.

The Applicant's Position:

The Applicant intends to provide data supporting the following claims:

- Encorafenib PK (plasma concentration profiles and PK parameters) in the BREAKWATER study were consistent with historical data in adult patients with *BRAF V600E*-mutant mCRC after prior therapy (NDA 210496/S-006, Sequence 0225).
- Participants receiving both encorafenib and oxaliplatin (EC + mFOLFOX6) had no evidence of overt changes in oxaliplatin PK, as measured as platinum in plasma and platinum in ultrafiltrate, suggesting that the drug-drug interaction risk between encorafenib and oxaliplatin is low and not clinically relevant.
- Oxaliplatin PK was not overtly changed with concurrent encorafenib administration (platinum AUC_{last} ratio of 1.12 and 1.04 in plasma and plasma ultrafiltrate, respectively in presence of encorafenib vs without concurrent encorafenib), which is consistent with the known metabolic pathways for oxaliplatin.
- These PK data support the use of the proposed dose of encorafenib 300 mg QD in combination with cetuximab 500 mg/m^2 Q2W and mFOLFOX6 for patients with *BRAF V600E*-mutant mCRC. The proposed dose for encorafenib is the same as the approved starting dose for encorafenib when in combination with cetuximab for the treatment of previously treated *BRAF V600E*-mutant mCRC.

The FDA's Assessment:
FDA agrees that encorafenib exposure following administration of a dosage of 300 mg QD in mCRC patients is consistent with historical results. The clinical pharmacology of encorafenib has been adequately characterized and the clinical pharmacology information submitted in the original NDA 210496 and supplements 6 and 13 were reviewed. As expected, based on the metabolic pathway for oxaliplatin, there is no DDI between encorafenib and oxaliplatin leading to altered exposure or either agent in BREAKWATER.

6.2.2. **General Dosing and Therapeutic Individualization**

6.2.2.1. **General Dosing**

Data:

The Applicant's Position:
The proposed dosing regimen for participants with *BRAF* V600E-mutant mCRC is encorafenib 300 mg QD in combination with cetuximab 500 mg/m^2 Q2W and mFOLFOX6. The proposed dose for encorafenib is the same as the approved starting dose for encorafenib when in combination with cetuximab for the treatment of previously treated *BRAF* V600E-mutant mCRC. The proposed cetuximab dosing regimen is consistent with clinical practice and with a labeled schedule for cetuximab (see Section 8.1.1 Dose selection). The proposed dosing regimen for the components of the mFOLFOX6 regimen are unchanged from current clinical practice.

The FDA's Assessment:
The proposed recommended dosage is 300 mg orally QD, with or without food, in combination with cetuximab 500 mg/m^2 IV Q2W dosage (current approved recommended dosage in combination with encorafenib) and mFOLFOX6. The proposed encorafenib dosage in combination with cetuximab and mFOLFOX6 is acceptable. Exposure-response (E-R) analysis did not indicate a relationship between encorafenib exposure and the ORR in the proposed patient population. E-R analysis for safety indicate a positive relationship between encorafenib exposure and Grade ≥3 adverse reactions; however, the current labeling for BRAFTOVI includes dosage modifications for Grade ≥3 adverse reactions. No relationship was observed between encorafenib exposure and all-grade AESIs (myelosuppression, cutaneous non-squamous cell carcinoma, facial paresis, hepatic failure, QT prolongation).

6.2.2.2. **Therapeutic Individualization**

Data:
Not applicable.

The Applicant's Position:
No new information is provided in the current submission. The relationship between exposures of encorafenib in combination with cetuximab with or without mFOLFOX6 and safety from BREAKWATER will be evaluated in the ER safety analysis and the results will be summarized in PMAR EQDD-C422f-sNDA-1571.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.2.2.3. **Outstanding Issues**

Data:
Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:
There were no outstanding issues identified in the review of this sNDA.

6.3. **Comprehensive Clinical Pharmacology Review**

6.3.1. **General Pharmacology and Pharmacokinetic Characteristics**

Data:
This data has been previously provided in prior encorafenib submissions.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Encorafenib exposure at the 300 mg QD dosage in combination with cetuximab and mFOLFOX6 in mCRC patients is consistent with historical results. There is no clinically relevant DDI between encorafenib and oxaliplatin that leads to altered exposure of either agent as expected, and observed, in BREAKWATER.

Further evaluation of the QTc effects of encorafenib at a dosage of 300 mg QD are not necessary from a clinical pharmacology perspective and QTc prolongation data in the current submission were not reviewed by FDA QT-IRT.

Pharmacokinetics

- The current sNDA includes new PK results from BREAKWATER for encorafenib in combination with cetuximab and mFOLFOX6. The PK for encorafenib, LHY746 (inactive metabolite of encorafenib), and oxaliplatin were assessed in the safety lead-in (n=27) that preceded the Phase 3 portion of the trial. Cycle 1 Day 1 and Cycle 1 Day 15 results are summarized in **Table 3.** The PK characteristics of encorafenib are consistent with historical results, including PK data submitted to NDA 210496 S-0006 for encorafenib in combination with cetuximab in patients with mCRC. Furthermore, oxaliplatin PK was not overtly changed with concurrent encorafenib administration (platinum AUC_{last} ratio of 1.1 and 1 in plasma and plasma ultrafiltrate, respectively in the presence of encorafenib vs without encorafenib), demonstrating no clinically relevant DDI between encorafenib and oxaliplatin, which is consistent with the known metabolic pathways for oxaliplatin.

Table 3: Descriptive Summary of Plasma PK Parameters of Encorafenib, LHY746, and Oxaliplatin (Safety Lead-in Cohort in Protocol C4221015 [BREAKWATER])

Analyte	C1D1		C1D15	
	Geometric Mean AUC_{last} (ng·h/mL) (%CV)	Geometric Mean C_{max} (ng/mL) (%CV)	Geometric Mean AUC_{last} (ng·h/mL) (%CV)	Geometric Mean C_{max} (ng/mL) (%CV)
Encorafenib	11,500 (88) (n=23)	2,870 (95) (n=23)	7,080 (37) (n=15)	2,320 (60) (n=16)
LHY746	2,440 (91) (n=23)	582 (84) (n=23)	3,770 (103) (n=15)	873 (82) (n=16)
Platinum in plasma-ultrafiltrate	6,060 (61) (n=25)	636 (41) (n=25)	5910 (20) (n=17)	697 (33) (n=17)

Source: Table 2 in the Applicant's Summary of Clinical Pharmacology

QT/QTc prolongation

- Encorafenib is associated with dose-dependent QTc interval prolongation. The results from a definitive evaluation of the effects of encorafenib on the QTc interval were included in the original NDA review. As exposures at the encorafenib dosage of 300 mg QD in patients with mCRC do not exceed those at the current approved encorafenib dosage of 450 mg QD, further QTc evaluation at the dosage of 300 mg QD is not necessary from a clinical pharmacology perspective. Furthermore, no new signal for QTcF > 500 ms was observed in patients with mCRC receiving encorafenib in combination with cetuximab and mFOLFOX6 in the BREAKWATER study as summarized in **Table 4.**

Table 4: Summary of Treatment-Emergent QT-Prolongation in BREAKWATER (DCO 22 Dec 2023)

	EC (N=150)	EC+mFOLFOX6 (N=222)	Standard of Care (N=206)
QTcF > 500 ms	3%	4%	1%
Increase from baseline > 30 ms	39%	43%	13%
Increase from baseline > 60 ms	6%	10%	3%

Source: Table 14.3.6.2.1 in Study C4221015 CSR in Module 5.3.5.1

6.3.2. **Clinical Pharmacology Questions**

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:
The approved dose in mCRC of encorafenib 300 mg QD was used in combination with cetuximab 500 mg/m^2 Q2W. The cetuximab regimen is consistent with clinical practice and with a labeled schedule for cetuximab (see Section 8.1.1 Dose selection). In BREAKWATER, the EC regimen was combined with the standard mFOLFOX6 regimen. Encorafenib PK (plasma concentration profiles and PK parameters) in participants with *BRAF* V600E-mutant mCRC in the BREAKWATER study were consistent with those described previously (NDA 210496/S-006, Sequence 0225) in adult patients with *BRAF* V600E-mutant mCRC after prior therapy. In addition, results from the population PK analysis conducted using data from the BREAKWATER study and encorafenib ER analyses for selected efficacy and safety endpoints from the BREAKWATER study will be provided in the final submission package.

The Applicant's Position:
The clinical pharmacology data supports the proposed starting dose of encorafenib 300 mg QD in combination with cetuximab 500 mg/m^2 Q2W and mFOLFOX6 for patients with *BRAF* V600E-mutant mCRC. Encorafenib PK in participants in the BREAKWATER study were consistent with those described previously for adult patients with *BRAF* V600E-mutant mCRC after prior therapy (NDA 210496/S-006, Sequence 0225). Participants receiving both encorafenib and oxaliplatin (EC + mFOLFOX6) had no evidence of overt changes in oxaliplatin PK as expected, based on a lack of overlapping metabolic pathways for encorafenib and oxaliplatin.

The FDA's Assessment:

FDA agrees with the Applicant's position. Overall, the efficacy data from the pivotal trial and E-R analyses for efficacy support the recommended starting dose of BRAFTOVI 300 mg QD. E-R analyses indicate that there are no evident E-R relationships between exposure and efficacy in BREAKWATER. Refer to **19.4.** OCP Appendices for a detailed review of E-R analyses and **Section 8.1** for a detailed review of efficacy.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:
This submission will include results from encorafenib popPK and ER analyses with key efficacy and safety endpoints, conducted using data from participants in the BREAKWATER study. These results are intended to support the encorafenib dosing for the combination regimen for this submission.

The proposed dose of 300 mg QD for encorafenib for the treatment of the target population in the current submission was approved in combination with cetuximab for adult patients with mCRC with a *BRAF* V600E mutation after prior therapy. The systemic exposures of encorafenib observed in BREAKWATER (given as EC and EC + mFOLFOX6) were consistent with those historically resulting in clinical activity in the previously treated mCRC population. In BREAKWATER, encorafenib was combined with cetuximab 500 mg/m^2 Q2W. This cetuximab

regimen is consistent with clinical practice and with a labeled schedule for cetuximab. The proposed dosing regimen for the components of the mFOLFOX6 regimen for this submission are unchanged from current clinical practice.

The Applicant's Position:
The PK results collected from the BREAKWATER study support the proposed dose of encorafenib 300 mg QD in combination with cetuximab 500 mg/m^2 Q2W and mFOLFOX6 (as per local prescribing information) for patients with *BRAF* V600E-mutant mCRC.

The FDA's Assessment:

FDA agrees that the proposed recommended dosage of encorafenib 300 mg orally QD in combination with cetuximab 500 mg/m^2 Q2W and mFOLFOX6 is acceptable for the treatment of *BRAF* V600E-mutant mCRC**.** FDA agrees that the PK characteristics of encorafenib are consistent with historical results, including PK data submitted to NDA 210496 S-0006 for encorafenib in combination with cetuximab in patients with mCRC. E-R results for safety are also consistent with previous E-R analyses conducted in patients with melanoma and mCRC, which indicate a positive relationship between encorafenib exposure and Grade ≥3 adverse reactions. The current labeling for BRAFTOVI includes dosage modifications for Grade ≥3 adverse reactions.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:
Relevant covariates were tested during the initial development of the population PK model for encorafenib and are described in the initial NDAs for melanoma (NDA 210496) and for mCRC (NDA 210496/S-006, Sequence 0225). These covariates included measures of renal and hepatic function, disease status, age, body weight, and ethnicity/race. No substantial differences based on visual inspection of relevant covariates and the magnitude of model covariate effect point estimates were noted in the popPK analyses supporting either the melanoma or mCRC indications.

The Applicant's Position:
Any required dose adjustment for individual patients based on intrinsic patient factors should follow the current approved label recommendations for encorafenib, cetuximab, oxaliplatin, leucovorin, and 5-FU.

The FDA's Assessment:
FDA agrees that dose individualization should follow the current approved product labeling for encorafenib, cetuximab, oxaliplatin, fluorouracil, and leucovorin.

FDA agrees no intrinsic (renal and hepatic function) factors appear to have clinically relevant effects on encorafenib exposure in patients with mCRC based on updated PopPK analysis. Age, mCRC tumor type, other tumor types, and body weight were identified as statistically significant covariates affecting encorafenib plasma exposure in the PopPK analysis, however, the expected change in encorafenib PK parameters based on these effects was estimated to be <20% and is therefore considered not clinically relevant.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:
The potential for drug-drug interactions between encorafenib and oxaliplatin was assessed in BREAKWATER. As expected, exposures for oxaliplatin were not changed with concurrent encorafenib administration. Additionally, encorafenib plasma exposures were consistent with those described previously for adult patients with *BRAF* V600E-mutant mCRC after prior therapy, indicating no change in encorafenib disposition in the presence of oxaliplatin.

The Applicant's Position:
In line with known metabolic pathways for the 2 drugs, encorafenib and oxaliplatin PK were unchanged when administered in combination. In addition, no new information regarding drug-food or drug-drug interactions was noted for the combination proposed in this submission.

The FDA's Assessment:
FDA agrees with the Applicant's position. Given that encorafenib is primarily metabolized by CYP3A4 and oxaliplatin undergoes extensive nonenzymatic biotransformation, there is no mechanistic reason to expect a drug-drug interaction between encorafenib and oxaliplatin. Therefore, as expected, there is no clinically relevant DDI between encorafenib and oxaliplatin that leads to altered exposure of either agent in BREAKWATER.

X	X
Primary Reviewer	Team Leader
Lily Leu, PharmD Da Zhang, Ph.D.	Jason Moore, PharmD Youwei Bi, Ph.D Stacy Shord, PharmD

7. Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 5. Applicant – Listing of Clinical Trials Relevant to this NDA/BLA

Protocol and NCT Number	Study Design and Endpoints	Treatment Groups	Number of Participants	Demographics	Duration of Treatment	Study Information
BREAKWATER (C4221015; NCT04607421): An Open-label, Multicenter, Randomized Phase 3 Study of First-line Encorafenib Plus Cetuximab with or without Chemotherapy versus Standard of Care Therapy with a Safety Lead-in of Encorafenib and Cetuximab Plus Chemotherapy in Participants with Metastatic *BRAF* V600E-Mutant Colorectal Cancer	Open-label, multicenter, 3-arm, randomized Phase 3 study of EC alone or in combination with mFOLFOX6 versus standard-of-care chemotherapy in first-line participants with *BRAF* V600E-mutant mCRC. Prior to Phase 3 portion of study, a 2-cohort SLI was conducted to evaluate safety/tolerability and PK of EC in combination with either FOLFIRI or mFOLFOX6 in participants with *BRAF* V600E-mutant mCRC who had ≤1 prior systemic regimen(s) for metastatic disease. Primary endpoints: • **Phase 3:** Compare the efficacy of EC + mFOLFOX6 (Arm B) vs standard of care (Control Arm [Arm C]), as measured by the primary endpoints of PFS by BICR and ORR by BICR, of Arm B versus Arm C.	**Phase 3** • EC Arm (Arm A): encorafenib 300 mg PO QD + cetuximab 500 mg/m^2 IV Q2W • EC + mFOLFOX6 Arm (Arm B): encorafenib 300 mg PO QD + cetuximab 500 mg/m^2 IV Q2W + mFOLFOX6 IV • Control Arm (Arm C): Investigator's choice of mFOLFOX6 ± bevacizumab, FOLFOXIRI ± bevacizumab, OR CAPOX ± bevacizumab	**Phase 3:** ***Full Analysis Set*** N: 637 EC Arm (N): 158 EC + mFOLFOX6 Arm (N): 236 Control Arm (N): 243 ***FAS, ORR Subset*** EC + mFOLFOX6 Arm (N): 110 Control Arm (N): 110 ***Safety Set*** N: 613 EC Arm (N): 154 EC + mFOLFOX6 Arm (N): 231 Control Arm (N): 228	**Phase 3:** ***Full Analysis Set*** Total: Sex (N): M: 321 F: 316 Age (yrs) Median (range): 61.00 (24 to 84) Race (N): W:373 A: 243 AI/AN: 1 B: 2 NR: 16 MR: 2	**Phase 3:** ***Safety Set*** EC Arm: Median (range) for regimen: 26.3 weeks (0.1 to 99.1 weeks) EC + mFOLFOX6 Arm: Median (range) for regimen: 28.1 weeks (1.3 to 107.4 weeks) Control Arm: Median (range) for regimen: 20.4 weeks (1.1 to 98.3 weeks)	• FPFV: 21 December 2020 • Data cutoff date (PCD): 22 December 2023 • 258 centers in 29 countries • Ongoing

Table 5. Applicant – Listing of Clinical Trials Relevant to this NDA/BLA

Protocol and NCT Number	Study Design and Endpoints	Treatment Groups	Number of Participants	Demographics	Duration of Treatment	Study Information
	Primary endpoint: • **SLI:** The number and proportion of participants experiencing DLTs during the DLT-evaluation period.	**SLI** • EC + mFOLFOX6 Cohort (Cohort 2): encorafenib 300 mg PO QD + cetuximab 500 mg/m^2 IV Q2W + mFOLFOX6 IV • EC + FOLFIRI Cohort (Cohort 1): encorafenib 300 mg PO QD + cetuximab 500 mg/m^2 IV Q2W + FOLFIRI IV	**SLI** ***Full Analysis Set/Safety Set*** N: 57 EC + mFOLFOX6 Cohort (N): 27 EC + FOLFIRI Cohort (N): 30	**SLI:** ***Full Analysis Set*** EC + mFOLFOX6 Cohort: Sex (N): M: 11 F: 16 Age (yrs) Median (range): 58.00 (28 to 78) Race (N): W:19 A: 8 AI/AN: 0 B: 0 NR:0 MR: 0 EC + FOLFIRI Cohort: Sex (N): M: 20 F: 10 Age (yrs): Median (range): 56.50 (37 to 77) Race (N): W: 23 A: 6 AI/AN: 0 B:1 NR:0 MR:0	**SLI** ***Safety Set*** EC + mFOLFOX6 Cohort: Median (range) for regimen (weeks): 37.9 (4.0 to 145.4) EC + FOLFIRI Cohort: Median (range) for regimen (weeks): 56.5 (2.0 to 147.3)	

The Applicant's Position:
The overview of efficacy (primary endpoint of ORR by BICR) and safety for this submission focuses on the statistically significant and clinically meaningful results from the Phase 3 portion of BREAKWATER (Study C4221015) and are sufficient to demonstrate the efficacy and safety of encorafenib in patients with *BRAF* V600E-mutant mCRC.

The FDA's Assessment:
FDA agrees with the Applicant's description of the BREAKWATER trial. The clinical data supporting the FDA's assessment of efficacy and safety were based on BREAKWATER.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. BREAKWATER (Study C4221015)

Trial Design

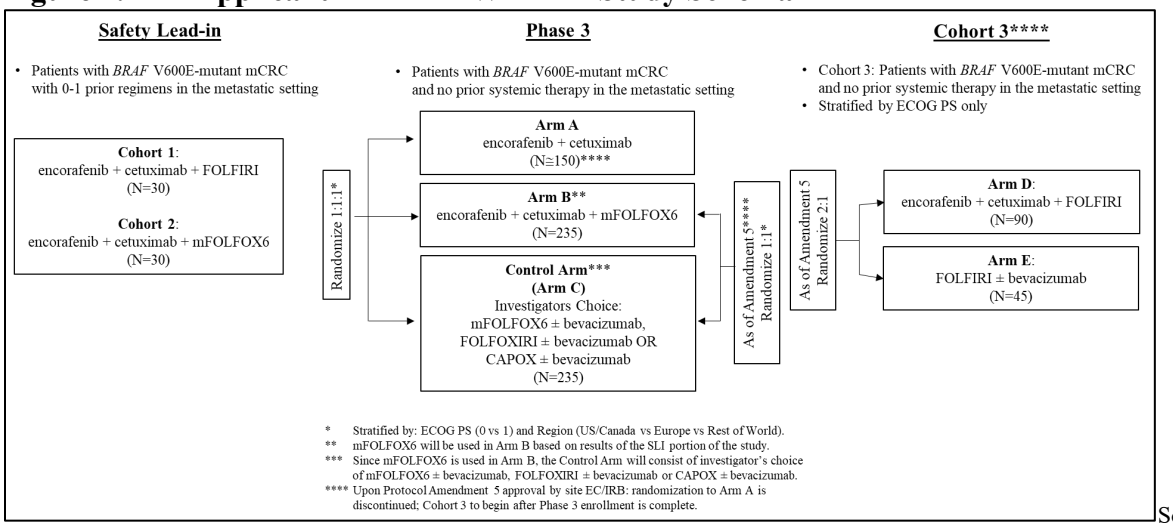
The Applicant's Description:
BREAKWATER is an open-label, multicenter, 3-arm, randomized Phase 3 study of EC alone (EC Arm) or in combination with chemotherapy (mFOLFOX6; EC + mFOLFOX6 Arm) versus standard-of-care chemotherapies (Control Arm: mFOLFOX6, FOLFOXIRI, or CAPOX each with or without bevacizumab) in first-line participants with *BRAF* V600E-mutant mCRC. Prior to the Phase 3 portion of the study, a 2-cohort SLI was conducted to evaluate the safety/tolerability and PK of EC in combination with standard-of-care chemotherapies (FOLFIRI or mFOLFOX6) in participants with *BRAF* V600E-mutant mCRC who had ≤1 prior systemic regimen(s) for metastatic disease. In addition to the Phase 3 portion, an open-label, 2-arm, randomized Cohort 3 portion is being conducted to evaluate EC in combination with FOLFIRI versus FOLFIRI with or without bevacizumab in first-line participants with *BRAF* V600E-mutant mCRC. Cohort 3 started after the enrollment of the Phase 3 portion was complete.

Treatment was to be administered until disease progression (confirmed by BICR in the Phase 3 portion), unacceptable toxicity, withdrawal of consent/assent, lost to follow-up, or death. After discontinuation of study intervention, participants were to be followed for survival and initiation of subsequent anticancer therapies/dates of progression, until withdrawal of consent/assent, the participant was lost to follow-up, death, or the final OS analyses.

This sNDA will focus on the Phase 3 ORR PCD results for the EC + mFOLFOX6 Arm and the Control Arm. The Phase 3 portion of the study initially included the EC Arm into which enrollment was discontinued with Protocol Amendment 5 (see Section 8.1.1 Assignment to treatment); thus, the EC Arm is included in relevant summary tables, but in-text discussions of the EC Arm are only presented in the CSR**.** In addition, safety data from the EC + mFOLFOX6 Cohort of the SLI is considered as supportive. Cohort 3 data are not presented.

Basic study design and Trial location:

Figure 1. Applicant - BREAKWATER Study Schema



Source: C4221015 - Report Body Figure 1

This study was conducted at 258 sites in 29 countries, including the US.

Study information, including study primary endpoints and site locations for the Phase 3 study is presented in Table 5. Study activities were conducted per protocol.

Screening assessments (eg, informed consent, demography/medical history, disease characteristics, treatment history, ECOG PS) were completed and reviewed to confirm that potential participants met all eligibility criteria.

Laboratory assessments were performed either locally or centrally per protocol. Disease assessments were performed at screening and every 6 weeks from the date of randomization for the first 18 months of treatment, then every 8 weeks thereafter until BICR-confirmed disease progression (regardless of new anticancer therapy for Phase 3), withdrawal of consent/assent, participant was lost to follow-up, death, or the final OS analysis.

Safety assessments were conducted per protocol. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant began from the time the participant provided informed consent/assent, which was obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention. Beyond 28 days after the last dose of study treatment, only SAEs considered related to study treatment were to be collected.

Diagnostic criteria: *BRAF* V600E mutation status was determined either locally prior to Screening (PCR- or NGS-based assay only, using either tumor tissue or blood) or centrally during Screening (using tumor tissue alone). Enrollment based on local assay results required confirmation of *BRAF* mutation status by a CAP/CLIA-certified central laboratory utilizing an

FDA approved test (Qiagen therascreen BRAF V600E RGQ PCR kit) within 30 days following first dose of study intervention.

Study treatments and Choice of control group: In Phase 3, participants were randomized to the following 3 treatment arms to receive:

- EC Arm (Arm A): encorafenib 300 mg QD +cetuximab 500 mg/m^2 Q2W (discontinued after enrollment of 158 patients due to Sponsor decision [see Section 8.1.1 Assignment to treatment]);
- EC + mFOLFOX6 Arm (Arm B): encorafenib 300 mg QD +cetuximab 500 mg/m^2 Q2W + mFOLFOX6;
- Control Arm (Arm C): one of the following per Investigator choice: mFOLFOX6 ± bevacizumab, FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab.

Encorafenib was self-administered orally once daily without regard to food. Encorafenib was to be taken daily in the morning at approximately the same time every day. Capecitabine, cetuximab, 5-FU, irinotecan, leucovorin, oxaliplatin, and bevacizumab were administered in accordance with their respective locally approved labels or per local institutional standards.

Treatment with Investigator's choice was chosen as the comparator in the Phase 3 portion of the study because a number of therapeutic options are available as initial therapy for mCRC, allowing selection of the regimen believed to potentially confer the greatest clinical benefit to a given participant. Currently, no treatment is indicated specifically for patients with *BRAF* V600E-mutant mCRC in the first-line setting and there is no single standard-of-care regimen established in this indication. Clinical guidelines established by ASCO, ESMO, and JSMO suggest that mFOLFOX6, FOLFIRI, FOLFOXIRI, or CAPOX are all acceptable therapeutic options and should be combined with bevacizumab where possible for initial treatment of patients with mCRC irrespective of tumor *BRAF* mutation status. The dose regimens used for capecitabine, 5-FU, irinotecan, leucovorin, oxaliplatin, and bevacizumab are consistent with the respective locally approved labels or local institutional standards.

Dose selection: In order to optimize the potential for benefit, while limiting the potential for toxicity, the starting encorafenib dose in the study was 300 mg QD, corresponding to its single-agent RP2D. This dose of encorafenib was administered in combination with cetuximab in Study ARRAY-818-302 (BEACON CRC) and was shown to be both effective and tolerable in participants with previously treated *BRAF* V600E-mutant mCRC. Based on these results, the approved dose of encorafenib for this indication is 300 mg QD when given in combination with cetuximab (BRAFTOVI [encorafenib] USPI, 2023).

Although the cetuximab regimen approved globally is 400 mg/m^2 first dose followed by 250 mg/m^2 IV weekly, a biweekly cetuximab regimen of 500 mg/m^2 was used in this study. The use of the biweekly regimen is fairly common in current practice and is included as an acceptable regimen in the NCCN guidelines (NCCN, 2024). This cetuximab dosing regimen is also consistent with a labeled schedule for cetuximab (ERBITUX [cetuximab], 2021). This regimen was selected in order to provide greater flexibility to study participants and was agreed with the FDA in the June 2020 Type B meeting.

Since the EC regimen had not previously been combined with cytotoxic chemotherapy, a SLI was conducted prior to the Phase 3 portion of the study to evaluate the safety/tolerability and PK of EC + mFOLFOX6 and EC + FOLFIRI. The results of the SLI informed which chemotherapy regimen was to be used in Arm B of the Phase 3 portion of the study. As a result of the SLI data review, Arm B consisted of EC in combination with mFOLFOX6.

Assignment to treatment: In the randomized Phase 3 portion of the study, initially participants were assigned at a ratio of 1:1:1 to receive EC (Arm A), EC + mFOLFOX6 (Arm B), or standard-of-care chemotherapy (Arm C; Control Arm), and then 1:1 to receive EC + mFOLFOX6 (Arm B) or standard-of-care chemotherapy (Arm C; Control Arm) after the approval of Protocol Amendment 5 (and discontinuation of enrollment of Arm A).

For the Phase 3 portion of the study, a randomization list stratified by ECOG (0 versus 1) and region (US/Canada versus Europe versus Rest of World) was used.

With Protocol Amendment 5, enrollment in EC Arm (Arm A) was discontinued because 1) preliminary antitumor activity, safety and tolerability observed with EC + mFOLFOX6 and EC + FOLFIRI in the SLI portion was encouraging (Tabernero et al, 2022b); 2) the probability to demonstrate superiority for EC versus standard-of-care chemotherapy was relatively low given the data from the ANCHOR-CRC study (NCT03693170), which showed comparable efficacy results of EC + binimetinib in comparison to historical chemotherapy (Van Cutsem et al, 2021); and 3) in general, *BRAF* V600E-mutant mCRC patients require a first-line regimen to control the aggressive tumor growth, supporting investigating EC + mFOLFOX6 or EC + FOLFIRI as potentially better treatment options in this patient population.

Blinding: This is an open-label study; however, the specific study intervention dispensed to the participant was assigned using an IRT. Treatment arm assignment was not blinded to Investigators and participants. The Sponsor (and its clinical trial team) was blinded to aggregate data summaries presented by treatment group. The BICR was blinded to participant treatment assignment throughout its operation.

Dose modification, dose discontinuation: Doses of encorafenib and cetuximab were to be interrupted or reduced for toxicity management following guidance provided in the protocol. Dose reductions beyond the permitted dose levels were not allowed for encorafenib or cetuximab. If encorafenib was permanently discontinued, participants were to permanently discontinue cetuximab. If cetuximab was permanently discontinued, participants were to permanently discontinue encorafenib if it was to be used as a single agent. Dose modifications for the chemotherapy agents and bevacizumab were also provided in the protocol and were based on the specific types of toxicities observed.

Administrative structure: An independent E-DMC reviewed cumulative safety data during the study conduct for the SLI, and Phase 3 as well as reviewed the efficacy at the interim analyses according to the charter. During the Phase 3 portion of the study, the E-DMC assessed safety/tolerability after the first 30 participants were randomized and treated for at least 1 cycle and then approximately every 6 or 12 months, as specified in the charter. The ORR and DOR

were evaluated by the E-DMC for Phase 3. A BICR was implemented to provide central assessments of tumor response**.**

Concurrent medications, dietary restrictions, and rescue medications:

The use of any concomitant medication/therapies deemed necessary for the care of the participant was permitted unless otherwise specified in the protocol. The following concomitant medications/therapies were prohibited:

- Additional anticancer agents such as cytotoxic chemotherapy, small-molecular targeted agents, biological agents, immune response modifiers or hormonal therapy.
- Investigational drugs, vaccines, and devices.
- Radiation therapy (not including palliative radiotherapy at local sites that covers ≤10% of the bone marrow reserve).
- Concomitant strong systemic CYP3A4 inhibitors.
- Concomitant moderate or strong systemic CYP3A4 inducers.
- Other medications were permitted, some with caution and/or action, as described in the protocol.
- Participants receiving encorafenib were instructed to avoid consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study intervention.
- There was no rescue medication in this study.

Treatment compliance:

Compliance was assessed by the Investigator and/or study personnel at each participant visit through review of participant diary entries, an accounting of returned study drug (ie, encorafenib or capecitabine, as applicable) and participant interviews.

Participant completion, discontinuation, and withdrawal:

A participant was to be permanently discontinued from study intervention for the following reasons: withdrawal of consent, unacceptable AEs/failure to tolerate study intervention, dose interruption required longer than permitted for each study drug due to an AE or clinically significant laboratory abnormality (>28 consecutive days for encorafenib; >2 missed consecutive doses of cetuximab; initiation of a new cycle or therapy during a cycle delayed for ≥4 weeks for mFOLFOX6/FOLFOXIRI; or initiation of a new cycle or therapy during a cycle delayed for ≥3 weeks for CAPOX), progressive disease (defined by RECIST, v1.1), participant became pregnant or began breastfeeding, lost to follow-up, death, and termination by sponsor. Participants who discontinued receipt of study intervention were to remain in the study and were to continue to be followed for protocol-specified follow-up procedures.

A participant was to be discontinued/withdrawn from the study for the following reasons: refused further follow-up (ie, withdrawal of consent), lost to follow-up, death, or study terminated by the sponsor or by the local health authority, IRB/IEC.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the BREAKWATER study design. FDA did not object to the choices of active comparator in the BREAKWATER trial and stated that choice of control arm therapy should be selected prior to randomization. FDA did not object to the discontinuation of the EC arm (Arm A) of the study based on preliminary data from the SLI portion of the study and external trial data suggesting comparable activity of EC in combination with binimetinib compared to historical control data for SOC chemotherapy.

FDA notes that the period for safety reporting and follow up in the BREAKWATER trial began from the time of informed consent through and including 28 days after the last dose of study treatment. Follow up beyond 28 days was done only for SAEs considered related to study treatment. FDA's normal convention for safety analysis include the period from treatment initiation through the study treatment period until 30 days after the last dose of study treatment. The difference in post-study treatment adverse event follow up conducted for the BEAKWATER trial and FDA normal convention for safety analysis is minimal and it not expected to significantly impact the interpretation of study.

In the June 12, 2020, Type B meeting FDA agreed that a supplemental PMA would not need to be submitted if the approved test, the Qiagen therascreen BRAF V600E RGQ PCR Kit, has not changed.

Eligibility Criteria

The Applicant's Description:

Phase 3 participants were aged ≥16 with histologically or cytologically confirmed colorectal adenocarcinoma that was Stage IV metastatic and who had a *BRAF* V600E mutation in tumor tissue or blood. Participants were also to have received no prior systemic regimens for metastatic disease. In addition, participants were to have measurable disease per RECIST, v1.1, as assessed by investigator and evidenced by available baseline scans, able to provide a sufficient amount of representative tumor specimen for central testing of *BRAF* V600E mutation status, an ECOG performance status of 0 or 1, and adequate bone marrow, hepatic, and renal function.

Previous treatment with any selective BRAF inhibitor or any EGFR inhibitor was prohibited. Participants must not have had concurrent or previous other malignancy within 2 years of study entry, active and uncontrolled viral and bacterial infections within 2 weeks prior to start of study intervention, or a history of chronic inflammatory bowel disease that required medical intervention ≤12 months prior to randomization. Participants with known DPD deficiency, *RAS*-mutant or unknown *RAS*-mutant colorectal adenocarcinoma, locally confirmed dMMR or MSI-H colorectal carcinoma or unknown MSI/MMR status unless unable to receive immune checkpoint inhibitors, presence of acute or chronic pancreatitis, leptomeningeal disease, impaired gastrointestinal function that may significantly alter the absorption of oral study intervention, clinically significant cardiovascular diseases, or symptomatic brain metastases were not eligible to enroll into the study.

The FDA's Assessment:

FDA agrees with this description of the eligibility criteria. The trial result cannot be extrapolated to patients with worse performance status as it is not clear if such patients would tolerate therapy similarly.

Study Endpoints

The Applicant's Description:

Primary and selected secondary efficacy endpoints:

Table 6. Applicant – BREAKWATER Study – Phase 3 Key Primary and Key Secondary Efficacy Endpoints Reported in this sNDA

Endpoint		Description	Analyses
Primary			
ORR by BICR		Proportion of participants who have achieved BOR of confirmed CR or PR per RECIST v1.1 as assessed by BICR.	Treatment effect of Arm B compared to Arm C, as measured by stratified odds ratio (99.8% and 95% CI), using Cochran-Mantel-Haenszel test stratified by randomization strata considering the first 110 randomized participants each in Arm B and in Arm C.
Key Secondary			
OS		Time from date of randomization to death due to any cause.	Treatment effect estimated using a Cox's proportional hazards model stratified by randomization strata to calculate HR for OS of Arm B vs Arm C. Comparison between Arm B and Arm C using a 1-sided stratified log-rank test. In order to account for the group sequential design on this endpoint, the repeated CI method will be used to construct the 2-sided repeated CI for the hazard ratio at the interim and the final analyses of OS.
Secondary (Descriptive Statistics Only)			
ORR by investigator, DOR, and TTR by BICR and investigator	ORR	Proportion of participants who have achieved a confirmed BOR of CR or PR per RECIST v1.1 as assessed by investigator.	ORR calculated along with corresponding 2-sided Wilson score 95% CI.
	DOR	Time from the date of first radiographic evidence of response (CR or PR) to the earliest documented disease progression per RECIST v1.1, or death due to any cause. DOR is calculated for participants with a confirmed response (CR or PR).	K-M estimate and median DOR time with 2-sided 95% CIs.

Table 6. Applicant – BREAKWATER Study – Phase 3 Key Primary and Key Secondary Efficacy Endpoints Reported in this sNDA

Endpoint		Description	Analyses
	TTR	Time from the date of randomization to first radiographic evidence of response (CR or PR) per RECIST v1.1. TTR is calculated for participants with a confirmed response (CR or PR).	TTR summarized using simple descriptive statistics (mean, standard deviation, median, minimum, maximum, first quartile, third quartile).

Source: C4221015 – Report Body Table 2

The FDA's Assessment:

FDA agrees with the description of study endpoints. ORR is a sign of anti-tumor activity as tumors generally do not shrink in the absence of therapy. An ORR difference of an acceptable magnitude has been used in oncology as an endpoint that may be reasonably likely to predict benefit.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Data for all participants were assessed to determine if participants met the criteria for inclusion in each analysis population prior to unblinding and releasing the database. Table 7 describes the population sets analyzed:

Table 7. Applicant – Definitions of the Populations Used for the Phase 3 Analyses

Participant Analysis Set	Description
FAS	The FAS included all participants who were randomized in the Phase 3 portion of the study. Participants were analyzed according to the study treatment assigned at randomization.
FAS, ORR Subset	For primary analysis of ORR/DOR/TTR in the Phase 3 portion of the study, "Full Analysis Set, ORR Subset" comprises the first 110 participants randomized in each Arm B and Arm C.
Central *BRAF* V600E Positive Analysis Set	All participants who were randomized in the Phase 3 portion of the study with a confirmed central laboratory result of *BRAF* V600E mutation. Participants were analyzed according to the study treatment assigned at randomization.
Safety Analysis Set	All participants who received at least 1 dose of study drug. Participants were analyzed according to the study treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period in which case participants were analyzed according to the actual study treatment received in the first cycle.

Table 7. Applicant – Definitions of the Populations Used for the Phase 3 Analyses

Participant Analysis Set	Description
PK Analysis Set	The PK concentration set is defined as all enrolled participants who were treated and had at least 1 analyte concentration. The PK parameter analysis set is defined as all enrolled participants treated who had sufficient information to estimate at least 1 of the PK parameters of interest and had no major protocol deviations affecting PK assessment. Participants were analyzed according to the actual study treatment received.

Source: C4221015 – SAP Version 6.0

Statistical methodology used to adjust for multiplicity

For the Phase 3 portion of the study, a hierarchical testing procedure was to be used to control the family-wise type I error rate.

Eight months after randomization of the first 110 participants each in Arm B and in Arm C, or after the completion of enrollment of the Phase 3 portion of the study, whichever occurred later, the ORR by BICR was compared for Arm B versus Arm C, on these first 220 participants, using a 1-sided alpha of 0.001.

Once at least 230 PFS events by BICR are observed for Arm B + Arm C and at least 12 months after the completion of enrollment of the Phase 3 portion of the study, the PFS analysis for the primary comparison of PFS by BICR for Arm B versus the Arm C will be tested using a 1-sided alpha of 0.023.

At the time of ORR and PFS analysis, if at least one of them is significant, an interim analysis for OS will be conducted, and hierarchical procedure for control of alpha for ORR/PFS and OS will be applied.

If the results of the interim analysis of OS are not statistically significant, a final OS analysis will be performed once 297 events are observed for Arm B + Arm C.

The overall significance level for Phase 3 portion of the study is 0.025 (1-sided) and was to be used as follows:

- 1-sided alpha of 0.001 for the comparison of ORR by BICR of Arm B versus Arm C;
- 1-sided alpha of 0.023 for the comparison of PFS by BICR of Arm B versus Arm C;
- alpha for the comparison of OS of Arm B versus Arm C will depend on the outcome of ORR and PFS;
- 1-sided alpha of 0.001 for the comparison of PFS by BICR of Arm A versus Arm C, even if there is no plan for formal testing.

No formal statistical testing was to be performed on the secondary and exploratory endpoints (with the exception of the key secondary endpoint described above), sensitivity analyses and subgroup analyses.

Pre-planned subgroup analyses

The following subset analyses were performed for ORR by BICR for Phase 3 FAS participants (Arm B vs. Arm C):

- Age (<65 years vs ≥65 years).
- [redacted] (Male vs Female).
- ECOG performance status based on the IRT system (0 vs 1).
- Number of organs involved at baseline (≤2 vs ≥3) according to BICR.
- Side of tumor (left vs right).
- Presence of liver metastases at baseline, based on Target and Non-target lesion assessment (yes vs no), according to BICR.

The BREAKWATER study original SAP had 6 amendments. The most significant modifications to the SAP are summarized in Table 8.

Table 8. Applicant - BREAKWATER Study Rationale for SAP Amendments

Version/ Issue Date	Overall Rationale for Amendment
1/ 09 Sep 2020	N/A – Original SAP
2/ 11 May 2021	Updated to align with protocol amendment 3 and to add analyses for Korea and Japan
3/ 26 Apr 2022	Updated to align with protocol amendment 4: Based on SLI results, primary and key endpoints for Phase 3 were modified. In addition, for the Phase 3 portion, efficacy endpoints based on investigator assessment were changed to derived investigator tumor assessment.
4/ 17 Feb 2023	Updated to align with Protocol Amendment 5 based on FDA input /discussion: reassigned Arm A key secondary endpoints to secondary endpoints, added ORR as primary endpoint for Phase 3, and added Cohort 3 with 2 randomized arms (Arms D and E).
5/ 15 Dec 2023	Reviewed after BDR to align with requested minor changes and manage particular cases.
6/ 08 March 2024	Updated the required number of PFS events for the final analysis and as a result, decreased the power for the sample size calculation for PFS of Phase 3.

Source: C4221015 – SAP Version 6.0

The FDA's Assessment:

The FDA agrees with the applicant's description of the statistical analysis plan (SAP) and the SAP amendments. In response to an Information Request from FDA (issued on April, 24, 2024) the Applicant confirmed that Protocol Amendment 6 (3/8/24) was made before the interim efficacy analysis and was not informed by the efficacy information of this study.

PFS as an endpoint in this trial may be acceptable in part because of the potential for patients to receive encorafenib and cetuximab in a later line setting. Consideration of an effect on PFS will

be contingent on the magnitude of effect, risk-benefit profile, and point estimate and KM curves for OS (e.g., to assess the potential for a detriment on OS).

Protocol Amendments

The Applicant's Description:

There were 6 amendments to the original protocol. Important modifications to the BREAKWATER protocol are outlined in Table 9. Overall, modifications to the protocol were intended to increase participant safety and optimize the study design.

Table 9. Applicant – BREAKWATER Study Protocol Important Modifications

Version/Issue Date	Overall Rationale for Amendment
Original/ 15 Jul 2020	N/A
1/ 07 Aug 2020	• Added that where recommended by local label or guidelines, participants were to be tested for DPD deficiency before initiating treatment with fluorouracil or capecitabine; and that the 5-FU dose used in the FOLFOXIRI regimen could be administered per local standard of care. • Clarified that levo-leucovorin could only be supplied in Japan.
2/ 12 Nov 2020	• Added information regarding the treatment of participants during the COVID-19 pandemic. • Modified male participant reproductive inclusion criteria in compliance with the SmPCs of oxaliplatin and 5-fluorouracil.
3/ 24 Feb 2021	• Aligned the protocol with dosing and patient management recommendations per locally approved labels and prescribing information.
4/ 28 Feb 2022	• Updated Arm B to consist of EC + mFOLFOX6; therefore, references to the use of FOLFIRI in Arm B and Arm C were removed throughout the protocol. • Updated the primary and key secondary endpoints, the statistical procedure to preserve overall study alpha and updated the sample size based on the SLI data showing the tolerability of EC and chemotherapy treatment.
5/ 20 Dec 2022	• Post consultation with the FDA, the Phase 3 overall study design was changed to allow for potential accelerated approval based on the ORR. • Enrollment in Arm A of Phase 3 was discontinued. • Cohort 3 was added to the study.
6/ 13 Mar 2024	• Modified the required number of PFS events by BICR needed to conduct the primary PFS analysis for the Phase 3 portion of the study to enable a timely readout of the PFS given a slower-than-expected accrual of events.

Source: C4221015 – Protocol Amendment 6

The FDA's Assessment:

The FDA agrees with the Applicant's description of the protocol amendments. According to the Applicant, Protocol Amendment 6 (3/8/24) was made before the interim efficacy analysis and was not informed by the efficacy information of this study.

8.1.2. **Study Results**

Compliance with Good Clinical Practices

The Applicant's Position:

The study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines, applicable ICH GCP guidelines, and applicable laws and regulations, including applicable privacy laws.

The FDA's Assessment:

FDA agrees with the Applicant's position. There was no evidence that compliance with GCP was violated during the conduct of the BREAKWATER trial.

Financial Disclosure

Data:

Financial disclosure information is provided in the Financial Disclosure section in Section 19.2.

The Applicant's Position:

The integrity of the BREAKWATER study data was not affected by the financial interest of the investigators.

The FDA's Assessment:

There was one investigator who disclosed financial interests or arrangements for the BREAKWATER trial. This investigator did not enroll any patients. The Applicant reports due diligence was performed to obtain financial disclosures from three investigators.

The Applicant reported that the following processes were instituted during the trial to minimize potential bias:

- Random treatment assignment using an Interactive Response Technology system
- Blinded independent central review of radiology images
- Monitoring of trial sites
- Internal inspection and study data querry
- Use of an external Data Monitoring Committee
- Internal review by the Applicant's Quality Control Group

FDA has determined that is unlikely that financial bias had an impact on the PCD analysis in the BREAKWATER trial.

Patient Disposition
Data:

Table 10. Applicant - Disposition Events Summary - Phase 3 Full Analysis Set (Protocol C4221015)

Number (%) of Participants	EC (N=158) n (%)	EC+mFOLFOX6 (N=236) n (%)	Control (N=243) n (%)
Disposition phase: treatment			
Participants Entered:	158 (100.0)	236 (100.0)	243 (100.0)
Discontinued	125 (79.1)	99 (41.9)	161 (66.3)
Reason for discontinuation			
Adverse event	9 (5.7)	11 (4.7)	22 (9.1)
Death	2 (1.3)	8 (3.4)	10 (4.1)
Progressive disease	97 (61.4)	49 (20.8)	77 (31.7)
Withdrawal by subject	8 (5.1)	13 (5.5)	28 (11.5)
Global deterioration of health status	5 (3.2)	8 (3.4)	4 (1.6)
Other	4 (2.5)	10 (4.2)	20 (8.2)
Ongoing	33 (20.9)	137 (58.1)	82 (33.7)
Disposition phase: long-term follow-up			
Participants Entered:	125 (79.1)	99 (41.9)	161 (66.3)
Discontinued	58 (36.7)	43 (18.2)	95 (39.1)
Reason for discontinuation			
Death	46 (29.1)	38 (16.1)	72 (29.6)
Lost to follow-Up	2 (1.3)	1 (0.4)	1 (0.4)
Withdrawal by subject	10 (6.3)	4 (1.7)	22 (9.1)
Ongoing	67 (42.4)	56 (23.7)	66 (27.2)

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Table 14.1.1.5.1 encorafenib is for Pfizer internal use.

The Applicant's Position:
As of the data cutoff date, 58.1% of participants in the EC + mFOLFOX6 Arm and 33.7% in the Control Arm remain in the treatment phase of the study.

- The most frequent (≥5% of participants) reasons for discontinuation of study treatment in the EC + mFOLFOX6 Arm were progressive disease (20.8%) and withdrawal by subject (5.5%); and in the Control Arm were progressive disease (31.7%), withdrawal by subject (11.5%), AE (9.1%), and other (8.2%).

- In the follow-up phase, the most frequent reason for discontinuation was death (16.1% EC + mFOLFOX6 Arm and 29.6% Control Arm).

The FDA's Assessment:
The FDA generally agrees with the Applicant's description of the patient disposition. Ninety-eight percent of patients randomized to the EC + mFOLFOX6 arm and 94% of patients randomized to the control arm received at least one dose of study treatment. There was a numerically higher number of patients that withdrew from the study during the treatment phase in the control arm compared to the EC + mFOLFOX6 arm (11.5% versus 5.5, respectively). Reasons for withdrawal for most patients on both arms were nonspecific (e.g. withdrew consent, refused continued treatment, patient unwillingness). Other reasons for withdrawal during the treatment phase on the EC + mFOLFOX6 arm included change to different treatment, intolerance of side effect profile, or complaints of distance to study site (n=2 each). Other reasons for withdrawal from the treatment phase on the control arm included desire to get treatment closer to home/study site too far (n=4), change to different treatment (n=2), patient randomized but not dosed (n=2), and intolerance of side effect profile (n=1). It appears unlikely that patient withdrawal during the treatment phase of BREAKWATER was a sufficient source of bias between the study arms to invalidate the results. Overall, the observed differences in patient disposition between the EC + mFOLFOX6 arm and the control arm e unlikely to have significantly impacted the interpretation of the trial results.

Protocol Violations/Deviations

Data:

- The percentage of participants with at least 1 important protocol deviation was similar in the EC + mFOLFOX6 and Control Arms (28.4% and 24.7%, respectively).
- The most frequent (≥5% of participants) important protocol deviations by category in the EC + mFOLFOX6 Arm were related to the investigational product (8.5%), use of concomitant medications (5.5%), inclusion/exclusion (5.5%), and safety reporting (5.1%); and in the Control Arm were related to safety reporting (6.6%), investigational product (6.2%), and procedures/tests (6.2%).

The Applicant's Position:
All protocol deviations were systematically reviewed by the study team to identify potentially important protocol deviations and were deemed to have a negligible impact on the prespecified endpoints, conduct of the study, and study results.

The FDA's Assessment:
FDA agrees with this description of protocol deviations. The higher proportion of protocol deviations in the EC + mFOLFOX6 arm are related to a slight numerical increase in protocol deviations related to concomitant medications and investigational product (e.g. IP dispensed outside of IRT system). These protocol deviations are unlikely to have had a meaningful impact on the interpretation of study results.

Table of Demographic Characteristics

Data:

Table 11. Applicant - Demographic Characteristics - Phase 3 Full Analysis Set (Protocol C4221015)

	EC (N=158)	EC+mFOLFOX6 (N=236)	Control (N=243)	Total (N=637)
Age (Years), n (%)				
< 18	0	0	0	0
18 - < 65	105 (66.5)	150 (63.6)	139 (57.2)	394 (61.9)
>= 65	53 (33.5)	86 (36.4)	104 (42.8)	243 (38.1)
>=75	14 (8.9)	16 (6.8)	24 (9.9)	54 (8.5)
Median (range)	59.00 (26, 84)	60.00 (24, 81)	62.00 (28, 84)	61.00 (24, 84)
Mean(SD)	57.79 (13.21)	57.95 (12.71)	59.38 (12.89)	58.46 (12.90)
[redacted] n (%)				
Male	79 (50.0)	123 (52.1)	119 (49.0)	321 (50.4)
Female	79 (50.0)	113 (47.9)	124 (51.0)	316 (49.6)
Race, n (%)				
Black or African American	1 (0.6)	0	1 (0.4)	2 (0.3)
American Indian or Alaska Native	1 (0.6)	0	0	1 (0.2)
Asian	64 (40.5)	88 (37.3)	91 (37.4)	243 (38.1)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	88 (55.7)	141 (59.7)	144 (59.3)	373 (58.6)
Other	0	0	0	0
Not reported	4 (2.5)	7 (3.0)	5 (2.1)	16 (2.5)
Multiracial	0	0	2 (0.8)	2 (0.3)
Ethnicity, n (%)				
Hispanic or Latino	16 (10.1)	28 (11.9)	30 (12.3)	74 (11.6)
Not Hispanic or Latino	131 (82.9)	187 (79.2)	201 (82.7)	519 (81.5)
Not reported	11 (7.0)	21 (8.9)	12 (4.9)	44 (6.9)
Racial Designation, n (%)				
Japanese	19 (12.0)	25 (10.6)	26 (10.7)	70 (11.0)
Korean	5 (3.2)	12 (5.1)	10 (4.1)	27 (4.2)
Chinese	38 (24.1)	48 (20.3)	52 (21.4)	138 (21.7)
Other	88 (55.7)	134 (56.8)	140 (57.6)	362 (56.8)
Missing	8 (5.1)	17 (7.2)	15 (6.2)	40 (6.3)

Age at Screening (years) as reported on CRF.
The denominator to calculate percentages is N, the number of participants in the full analysis set within each treatment group.
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Table 14.1.2.1.1 encorafenib is for Pfizer internal use.

The Applicant's Position:
Demographics were generally similar between participants in the EC + mFOLFOX6 Arm and the Control Arm.

The FDA's Assessment:
The FDA agrees with the demographic data presented for the analysis population and agrees that these characteristics were generally balanced across the EC + mFOLFOX6 and control arms. The median age of patients in the BREAKWATER trial (including patients enrolled in the EC arm) was 61 years. The median age observed in BREAKWATER is slightly lower than the reported median age among patients with new cases of colorectal cancer (across cancer stages) in the SEER data (SEER 22). However, some publications have observed an increasing trend in colorectal cancer diagnoses in younger patients and a decreasing trend in patients 65 years and older (Vassilev 2022, ACS CRC Facts 2023).

This trial included few patients of Black/African American, American Indian/Alaskan Native, or Native Hawaiian/Pacific Islander race, with most patients enrolled to the study being of White or Asian race. Cases per 100,000 of new cases of colorectal cancer are numerically higher in American Indian/Alaska Native patients (48.6) and Black patients (41.7) than in White patients (35.7). Cases per 100,000 of new cases of colorectal cancer are reported collectively for Asian and Pacific Islander patients (28.6) (ACS CRC Facts 2023). While there was higher enrollment of patients who reported Latino ethnicity, there may still be some underrepresentation of these patients based on cases per 100,000 of new cases of colorectal cancer (32.5). Data is limited regarding racial and ethnic distribution in patients with BRAF V600E-mutated CRC.

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)
Data:

Table 12. Applicant - Baseline and Disease Characteristics - Phase 3 Full Analysis Set (Protocol C4221015)

Category	EC (N=158) n (%)	EC+mFOLFOX6 (N=236) n (%)	Control (N=243) n (%)
Body Site, n (%)			
Colon, Ascending	46 (29.1)	78 (33.1)	72 (29.6)
Colon, Descending	15 (9.5)	17 (7.2)	16 (6.6)
Colon, Rectosigmoid	11 (7.0)	17 (7.2)	16 (6.6)
Colon, Sigmoid	25 (15.8)	30 (12.7)	32 (13.2)

Table 12. Applicant - Baseline and Disease Characteristics - Phase 3 Full Analysis Set (Protocol C4221015)

Category	EC (N=158) n (%)	EC+mFOLFOX6 (N=236) n (%)	Control (N=243) n (%)
Colon, Transverse	26 (16.5)	39 (16.5)	35 (14.4)
Colon, Hepatic Flexure	6 (3.8)	9 (3.8)	14 (5.8)
Colon, Splenic Flexure	1 (0.6)	1 (0.4)	7 (2.9)
Rectum	17 (10.8)	24 (10.2)	27 (11.1)
Cecum	11 (7.0)	21 (8.9)	24 (9.9)
Side of Tumor, n (%)			
Left	69 (43.7)	89 (37.7)	98 (40.3)
Right	89 (56.3)	147 (62.3)	145 (59.7)
Stage at Initial Diagnosis, n (%)			
Stage I	4 (2.5)	3 (1.3)	2 (0.8)
Stage II	7 (4.4)	13 (5.5)	10 (4.1)
Stage III	24 (15.2)	37 (15.7)	43 (17.7)
Stage IV	123 (77.8)	183 (77.5)	188 (77.4)
Primary Tumor Resection, n (%)			
Completely Resected	82 (51.9)	116 (49.2)	105 (43.2)
Partially Resected	9 (5.7)	14 (5.9)	13 (5.3)
No Resection	67 (42.4)	106 (44.9)	125 (51.4)
Number of Organs Involved, n (%)			
<= 2	86 (54.4)	122 (51.7)	129 (53.1)
>= 3	72 (45.6)	114 (48.3)	114 (46.9)
Presence of Liver Metastases, n (%)			
Yes	94 (59.5)	144 (61.0)	156 (64.2)
No	64 (40.5)	92 (39.0)	87 (35.8)
Time Since Initial Diagnosis (months)			
Median (Range)	1.87 (0, 163)	1.94 (0, 112)	1.84 (0, 124)
Mean(SD)	7.91 (19.79)	6.81 (13.18)	7.26 (15.51)
Time Since Recurrence/Metastatic (months)			
Median (Range)	1.48 (0, 25)	1.54 (0, 40)	1.51 (0, 34)
Mean(SD)	2.18 (3.26)	2.25 (3.69)	2.04 (2.97)
ECOG PS at Baseline, n (%)			
0	79 (50.0)	129 (54.7)	131 (53.9)
1	74 (46.8)	103 (43.6)	98 (40.3)
Missing	5 (3.2)	4 (1.7)	14 (5.8)
BRAF V600E Status, Tumor Tissue (Central), n (%)			
Detected	150 (94.9)	226 (95.8)	224 (92.2)
Indeterminate	1 (0.6)	0	1 (0.4)

Table 12. Applicant - Baseline and Disease Characteristics - Phase 3 Full Analysis Set (Protocol C4221015)

Category	EC (N=158) n (%)	EC+mFOLFOX6 (N=236) n (%)	Control (N=243) n (%)
Not Detected	0	4 (1.7)	2 (0.8)
Not Available	7 (4.4)	6 (2.5)	16 (6.6)
BRAF V600E Status (Local), n (%)			
Detected	144 (91.1)	222 (94.1)	219 (90.1)
Not Detected	1 (0.6)	0	0
Not Available	13 (8.2)	14 (5.9)	24 (9.9)
KRAS Mutation Status (Local), n (%)			
Indeterminate	0	0	1 (0.4)
Not Detected	152 (96.2)	231 (97.9)	228 (93.8)
Not Available	6 (3.8)	5 (2.1)	14 (5.8)
NRAS Mutation Status (local), n (%)			
Detected	0	0	1 (0.4)
Not Detected	152 (96.2)	230 (97.5)	228 (93.8)
Not Available	6 (3.8)	6 (2.5)	14 (5.8)
MSI/MMR Status (local), n (%)			
MSI-H/dMMR	0	1 (0.4)	0
MSS/pMMR	151 (95.6)	229 (97.0)	227 (93.4)
Not Available	7 (4.4)	6 (2.5)	16 (6.6)
CEA at Baseline (ug/L), n (%)			
<= 5 ug/L	51 (32.3)	65 (27.5)	63 (25.9)
> 5 ug/L	101 (63.9)	166 (70.3)	163 (67.1)
Missing	6 (3.8)	5 (2.1)	17 (7.0)
Median (Range)	12.80 (1, 3837)	13.60 (1, 6236)	17.35 (1, 11132)
Mean(SD)	160.0 (494.9)	149.9 (547.7)	226.0 (912.5)
CRP at Baseline (mg/L), n (%)			
<= 10 mg/L	91 (57.6)	125 (53.0)	119 (49.0)
> 10 mg/L	61 (38.6)	105 (44.5)	107 (44.0)
Missing	6 (3.8)	6 (2.5)	17 (7.0)
Median (Range)	6.75 (0, 289)	8.20 (0, 209)	8.50 (0, 284)
Mean(SD)	26.80 (43.35)	23.72 (36.09)	29.49 (44.05)

Number of organs and presence of liver metastases are is based on BICR data for Ph3 and Investigator data for SLI.
Local testing can be performed by tumor or blood-based assays.
MSI status of MSS/pMMR includes MSI-L.
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:51) Source Data: adsl Table Generation: 16APR2024 (15:15) (Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR
PCD/C4221015 PH3 20240319 Unblinded/adsl s009 p3
Table 14.1.2.2.1 encorafenib is for Pfizer internal use.

The Applicant's Position: Disease and baseline characteristics were generally similar between participants in the EC + mFOLFOX6 Arm and the Control Arm.

Of 585 participants who had a *BRAF* V600E mutation per local result, 571 (97.6%) participants had the *BRAF* mutation confirmed by central testing, 6 participants had no mutation detected by central testing (1.0% discordance), and 2 participants had a central testing result that was indeterminate (ie, if there was no neoplastic cell in the tumor tissue submitted for analysis or if the test result was not qualified).

The FDA's Assessment:
The FDA agrees with the Applicant's description of other baseline characteristics. These baseline characteristics are generally balanced between the EC + mFOLFOX6 arm and the control arm. However there was a numerical difference in several disease characteristics including the presence of liver metastases (61% in the EC + mFOLFOX6 arm versus 64.2% in the control arm), number of patients with completely resected disease (49.2% in the EC + mFOLFOX6 arm versus 43.2% in the control arm), number of patients with no resection (44.9% in the EC + mFOLFOX6 arm versus 51.4% in the control arm), number of organs involved ≥3 (48.3% in the EC + mFOLFOX6 arm versus 46.9% in the control arm), and ECOG performance status of 1 (43.6% in the EC + mFOLFOX6 arm versus 40.3% in the control arm). Overall, these numeric differences in baseline disease characteristics are unlikely to have had a clinically significant impact on the interpretation of study results.

BRAF mutation status was tested in all patients enrolled in the EC + mFOLFOX6 arm and the control arm. *BRAF* mutations were detected in a higher proportion of patients in the EC + mFOLFOX6 arm when both central and local testing was conducted.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Data:
Treatment Compliance

Compliance with study intervention was documented in the source documents and CRF. Study intervention start dates, reasons for delays, dose reductions, and/or missed doses were recorded in the CRF. Deviations from the prescribed dosage regimen were recorded in the CRF. A record of study intervention dispensed to and administered to each participant was maintained.

Prior and Concomitant Medications

The percentage of participants with prior anticancer therapies was similar between the EC + mFOLFOX6 Arm and the Control Arm.

- The percentage of participants who received at least 1 prior adjuvant/neoadjuvant therapy was 14.8% EC + mFOLFOX6 Arm and 13.2% Control Arm.
- The percentage of participants who received at least 1 prior anticancer radiotherapy was 3.8% EC + mFOLFOX6 Arm and 2.1% Control Arm.

- The percentage of participants who received at least 1 prior anticancer surgery (excluding biopsy) was 57.6% EC + mFOLFOX6 Arm and 54.3% Control Arm.

The overall use of concomitant medications was 99.6% EC + mFOLFOX6 Arm and 99.6% Control Arm.

Rescue Medication Use: Not applicable

The FDA's Assessment:
The FDA generally agrees with the Applicant's position. The reported median relative dose intensity in the EC + mFOLFOX6 arm for encorafenib was 91.7% (range: 3% to 100.7%).

The Applicant reported the use of concomitant medications in the EC + mFOLFOX6 and control arms presented by preferred term. The most commonly used concomitant medications (>80%) were classified as ophthalmologicals, stomatological preparations, dermatologic corticosteroid preparations, vasoprotectives, systemic corticosteroids, otologicals, and nasal preparationsThe use of concomitant medications was generally balanced between the two treatment arms, however FDA notes a relatively larger numeric difference in the use of antipruritics (77% vs 40%) and antihistamines (75% vs 40%) in the EC + mFOLFOX6 arm compared to the control arm (potentially a reflection of the use of cetuximab).

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)
Data:
Efficacy Analysis of Primary Endpoint: ORR by BICR for EC + mFOLFOX6 vs Control

A summary of BOR and ORR (confirmed) based on BICR assessment is provided in Table 13.

- The primary analysis of ORR was performed using the Phase 3 FAS, ORR Subset using the pre-specified alpha level for significance of 0.001.
- The EC + mFOLFOX6 Arm met the primary endpoint of ORR demonstrating clinically meaningful and statistically significant improvement in confirmed ORR by BICR compared with the Control Arm (60.9% [95% CI: 51.6, 69.5] vs 40.0% [95% CI: 31.3, 49.3], respectively; odds ratio = 2.443 [95% CI: 1.348, 4.380] [99.8% CI: 0.989, 6.089], 1-sided p-value = 0.0008; 1-sided alpha=0.001).
- BOR of confirmed CR or PR by BICR was observed in 3 (2.7%) and 64 (58.2%) participants in the EC + mFOLFOX6 Arm and 2 (1.8%) and 42 (38.2%) participants in the Control Arm, respectively.

Sensitivity Analyses of Primary Endpoint Analysis: A sensitivity analysis of OR by BICR based on the Central *BRAF* V600E Positive Analysis Set yielded odds ratios and ORR values similar to the primary ORR analysis, reflecting the robustness of the benefit.

Subgroup Analysis of Primary Efficacy Endpoint: Consistent treatment effect favoring the EC + mFOLFOX6 Arm was observed across pre-specified subgroups.

Table 13. Applicant - Summary of Best Overall Response and ORR (Confirmed) Based on BICR Assessment (RECIST v1.1) - Phase 3 EC+mFOLFOX6 and Control Arms ORR Subset Full Analysis Set (Protocol C4221015)

	EC+mFOLFOX6 (N=110)	Control (N=110)
Confirmed Best Overall Response, n (%)		
Complete response	3 (2.7)	2 (1.8)
Partial response	64 (58.2)	42 (38.2)
Stable disease	31 (28.2)	34 (30.9)
Non-CR/Non-PD	3 (2.7)	4 (3.6)
Progressive disease	3 (2.7)	9 (8.2)
Not evaluable	6 (5.5)	19 (17.3)
Reason for Not Evaluable, n (%)		
No adequate baseline assessment	0	2 (1.8)
No post-baseline assessments due to early death	2 (1.8)	5 (4.5)
No post-baseline assessments due to other reasons	4 (3.6)	9 (8.2)
Stable disease too early [	0	3 (2.7)
Objective Response (CR+PR), n (%)	67 (60.9)	44 (40.0)
95% CI [1]	51.6, 69.5	31.3, 49.3
Stratified analysis of Objective Response Rate [2]| Comparison vs Control		
Odds Ratio	2.443	
95% CI [3]	1.348, 4.380	
99.8% CI [3]	0.989, 6.089	
1-sided p-value [4]	0.0008	
2-sided p-value [4]	0.0015	

[1] Wilson method used.
[2] Stratified by ECOG PS by Randomization , Geographic Region by Randomization factors.
[3] Odds ratio is estimated using Mantel-Haenszel method. Odds Ratio > 1 indicates better outcome for EC+mFOLFOX6 compared to Control; exact CI is calculated.
[4] P-value based on Cochran-Mantel-Haenszel (CMH) test.
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:54) Table Generation: 15APR2024 (19:19)
(Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR
PCD/C4221015 PH3 20240319 Unblinded/adrsb borc s001 p3bc
Table 14.2.1.3.1.1 encorafenib is for Pfizer internal use.

The Applicant's Position: Efficacy data from the randomized Phase 3 portion of BREAKWATER demonstrated a clinically meaningful and statistically significant improvement in confirmed ORR by BICR for the EC + mFOLFOX6 Arm compared to the Control Arm in first-line participants with *BRAF* V600E-mutant mCRC.

The FDA's Assessment:
The FDA generally agrees with the Applicant's description of the efficacy results of the primary endpoint. At the time of this data cutoff, enrollment of the Phase 3 portion of study was complete

and the first 220 number of patients (110 per arm) who were followed for a minimum of 8 months were included in the analysis of ORR. The control arm includes the following control drugs per investigator choice: mFOLFOX6 ± bevacizumab, FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab. The exploratory ORR results vary by the investigator choice of control therapy as shown in FDA Table 14, with the highest ORR of 54.5% for FOLFOXIRI+bevacizumab. Although exploratory, this effect is expected based on literature showing higher response rates of FOLFOXIRI (+/- bevacizumab) as compared to doublet therapy. Nevertheless, triplet therapy is reserved for the most fit patients and in practice patients may receive doublet or triplet therapy, and therefore the overall control (investigator's choice) was appropriate and the overall comparison acceptable.

At the time of this data cutoff of the BREAKWATER study, no analyses of the co-primary endpoint of PFS were conducted. The study is ongoing and the formal analysis of PFS will occur as pre-specified in the statistician plan.

Table 14: ORR by control arm treatment choice

ORR (n/N)	With Bevacizumab	Without Bevacizumab
CAPOX	39.1% (9/23)	20% (1/5)
FOLFOXIRI	54.5% (12/22)	0% (0/2)
mFOLFOX6	47.7% (21/44)	14.3% (1/7)

Data Quality and Integrity

The Applicant's Position:

There were no issues related to data quality and integrity. The sponsor or delegate provided study instruction and monitored the study through routine center visits to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data.

Overall, the impact of the COVID-19 pandemic was minimized through the adjustments and mitigations to ensure both participant safety and data integrity. There was no significant impact to the overall data quality and integrity of the study due to the changes associated with the COVID-19 pandemic.

There was also no significant impact to the overall data quality and integrity of the study due to the Ukraine/Russia war.

The robustness of the ORR results was confirmed by several pre-specified sensitivity and subgroup analyses, which yielded results consistent with the primary analysis.

The FDA's Assessment:

In general, the data quality is acceptable. The FDA reviewer was able to reproduce the efficacy results based on the submitted AdaM dataset for the BREAKWATER trial.

Efficacy Results – Secondary and other relevant endpoints

Data:

Key Secondary Efficacy Endpoint Analysis

OS

OS was not mature at the time of the data cutoff, with deaths occurring in a total of 112 participants in the FAS (40 participants [16.9%] in the EC + mFOLFOX6 Arm and 72 participants [29.6%] in the Control Arm) (Table 15).

- Median duration of follow-up for OS in the EC + mFOLFOX6 Arm was 10.3 months (95% CI: 8.6, 11.6); and in the Control Arm was 9.8 months (95% CI: 7.5, 11.3).
- The hazard ratio for death was 0.47 (95% CI: 0.318, 0.691, RCI: 0.166, 1.322) p-value = $4.5*10^{-5}$. A Kaplan-Meier plot of OS is provided in Figure 2.
- The Lan-DeMets (O'Brien-Fleming) boundaries for OS at this interim analysis, with the observed 37.7% of OS information fraction (112 OS events), was p-value = $8.3*10^{-8}$ (HR = 0.372).

Other Secondary Efficacy Endpoint Analyses

ORR by Derived Investigator Assessment

Confirmed ORR by derived Investigator assessment (64.5% [95% CI: 55.3, 72.9] for EC + mFOLFOX6 Arm vs 40.0% [95% CI: 31.3, 49.3] for Control Arm; odds ratio = 2.828 [95% CI: 1.548, 5.040]) was similar to the primary ORR analysis, reflecting the robustness of the benefit.

- The agreement rates between BICR and derived Investigator responses were for objective response were 85.5% and 87.3% for the EC + mFOLFOX6 Arm and Control Arm, respectively.

DOR

DOR based on BICR assessment is summarized in Table 16.

Objective responses by BICR in the EC + mFOLFOX6 Arm were durable and clinically meaningful compared with the Control Arm.

- The median DOR by BICR for responding participants in the EC + mFOLFOX6 Arm was 13.9 months (95% CI: 8.5, NE); and in the Control Arm was 11.1 months (95% CI: 6.7, 12.7), with 37.3% and 11.4% of the responding participants still ongoing without subsequent progression or death, respectively (Table 16).
- Of the objective responders, 68.7% EC + mFOLFOX6 Arm and 34.1% Control Arm had an objective response by BICR lasting ≥6 months, and 22.4% and 11.4% had responses, respectively, lasting ≥12 months.

TTR

Objective responses by BICR in the EC + mFOLFOX6 Arm were rapid.

- The median TTR by BICR in the EC + mFOLFOX6 Arm was 7.1 weeks (range: 5.7, 53.7) and in the Control Arm was 7.3 weeks (range: 5.4, 48.0), both corresponding to the approximate time of the first on-treatment tumor scan.

Table 15. Applicant - Summary of Overall Survival - Phase 3 EC+mFOLFOX6 and Control Arms Full Analysis Set (Protocol C4221015)

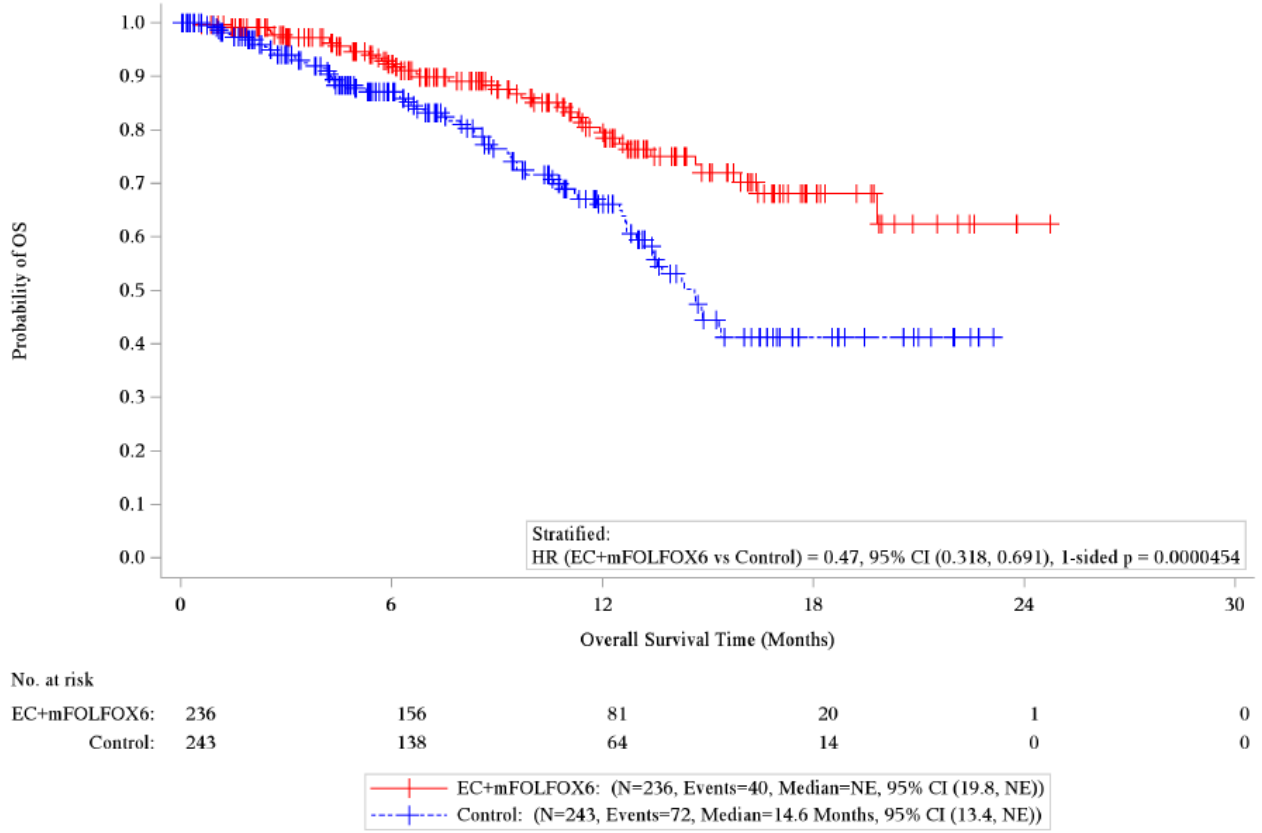
	EC+mFOLFOX6 (N=236)	Control (N=243)
Participants with event, n (%)	40 (16.9)	72 (29.6)
Death due to COVID-19	1 (0.4)	0
Participants censored, n (%)	196 (83.1)	171 (70.4)
Reason for censoring, n (%)		
Withdrawal of consent	4 (1.7)	22 (9.1)
Lost to follow-up [1]	1 (0.4)	1 (0.4)
Alive	191 (80.9)	148 (60.9)
Probability of being event-free (95% CI) [2]		
at 6 months	0.923 (0.875, 0.953)	0.871 (0.816, 0.911)
at 12 months	0.795 (0.717, 0.853)	0.661 (0.576, 0.733)
at 18 months	0.681 (0.575, 0.766)	0.412 (0.309, 0.513)
at 24 months	0.624 (0.471, 0.745)	NE (NE, NE)
at 30 months	NE (NE, NE)	NE (NE, NE)
at 36 months	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]		
Q1	14.7 (11.5, NE)	9.4 (8.1, 11.3)
Median	NE (19.8, NE)	14.6 (13.4, NE)
Q3	NE (NE, NE)	NE (NE, NE)
Stratified analysis [4] Comparison vs Control		
Hazard Ratio [5]	0.47	
95% CI [5]	0.318, 0.691	
RCI [6]	0.166, 1.322	
1-sided p-value [7]	0.0000454	
2-sided p-value [7]	0.0000908	

Table 15. Applicant - Summary of Overall Survival - Phase 3 EC+mFOLFOX6 and Control Arms Full Analysis Set (Protocol C4221015)

	EC+mFOLFOX6 (N=236)	Control (N=243)

[1] Includes participants deemed to be lost to follow-up by the Investigator
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] Based on the Brookmeyer and Crowley method.
[4] Stratified by ECOG PS by Randomization and Geographic Region by Randomization
[5] Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of EC+mFOLFOX6 compared to Control;
[6] Repeated confidence interval method used to take into account the group-sequential nature of the design as per EAST v 6.5.
[7] p-value from the log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:54) Table Generation: 15APR2024 (19:22)
(Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR
PCD/C4221015 PH3 20240319 Unblinded/adtte os s001 p3bc
Table 14.2.1.2.1.1 encorafenib is for Pfizer internal use.

Figure 2. Applicant - KM Plot Overall Survival - Phase 3 EC+mFOLFOX6 and Control Arms Full Analysis Set (Protocol C4221015)



CI from Brookmeyer and Crowley.
Stratified by ECOG PS and Region.
Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of EC+mFOLFOX6 compared to Control.
p-value based on stratified log-rank test.
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:54) Table Generation: 15APR2024 (19:22)
(Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR PCD/C4221015_PH3_20240319_Unblinded/adtte_os_f001_p3bc
Figure 14.2.1.2.1.1 encorafenib is for Pfizer internal use.

Table 16. Applicant - Summary of Duration of Response Based on BICR Assessment (RECIST v1.1) - Phase 3 EC+mFOLFOX6 and Control Arms ORR Subset Full Analysis Set (Confirmed Responders) (Protocol C4221015)

	EC+mFOLFOX6 (N=67)	Control (N=44)
Participants with event, n (%)	29 (43.3)	17 (38.6)
Type of event, n (%)		
Progressive disease	26 (38.8)	16 (36.4)
Death	3 (4.5)	1 (2.3)
Participants censored, n (%)	38 (56.7)	27 (61.4)
Reason for censoring, n (%)		
No adequate baseline assessment	0	0
Start of new anti-cancer therapy	11 (16.4)	17 (38.6)
Event after >=2 missing or inadequate post-baseline assessments	1 (1.5)	2 (4.5)
Withdrawal of consent	1 (1.5)	3 (6.8)
Lost to follow-up	0	0
No adequate post-baseline tumor assessment	0	0
Ongoing without an event	25 (37.3)	5 (11.4)
Probability of being event-free (95% CI) [1]		
at 3 months	0.968 (0.878, 0.992)	0.881 (0.714, 0.954)
at 6 months	0.829 (0.705, 0.904)	0.700 (0.494, 0.834)
at 9 months	0.623 (0.481, 0.736)	0.500 (0.285, 0.683)
at 12 months	0.511 (0.366, 0.639)	0.357 (0.151, 0.571)
at 15 months	0.468 (0.314, 0.608)	0.268 (0.082, 0.499)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]		
Q1	7.1 (5.9, 9.1)	5.5 (3.0, 8.3)
Median	13.9 (8.5, NE)	11.1 (6.7, 12.7)
Q3	NE (15.2, NE)	19.8 (11.1, NE)
Duration of Response, months		
Median (range)	8.5 (1.4, 22.1)	4.1 (1.2, 20.0)
Duration of Response Category, n (%)		
>= 6 months	46 (68.7)	15 (34.1)
>= 9 months	32 (47.8)	8 (18.2)
>= 12 months	15 (22.4)	5 (11.4)
>= 15 months	10 (14.9)	2 (4.5)

[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] Based on the Brookmeyer and Crowley method.
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:54) Table Generation: 15APR2024 (19:21)
(Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR PCD/C4221015_PH3_20240319_Unblinded/adtteb_dorc_s001_p3bc
Table 14.2.1.4.1.1 encorafenib is for Pfizer internal use.

The Applicant's Position:

- OS was not mature at the data cutoff date, with 40 (16.9%) deaths in the EC + mFOLFOX6 Arm and 72 (29.6%) deaths in the Control Arm, but no detrimental effect was observed with EC + mFOLFOX6 vs the control therapy (HR 0.47, 95% CI: 0.318, 0.691).
- Objective responses by BICR in the EC + mFOLFOX6 Arm were rapid, durable, and clinically meaningful compared with the Control Arm.

The FDA's Assessment:
The FDA agrees with the Applicant's description of the results of the secondary and other relevant endpoints. Although OS was not mature (37.7% of the deaths required for the final analysis), a positive trend in OS comparing the treatment arm to the control arm is observed. FDA notes that the secondary endpoints of ORR by derived investigator assessment and TTR are descriptive only and should be interpreted with caution.

Dose/Dose Response

Data:
See Clinical Pharmacology Section 6.3.2.1 and efficacy and safety data tables in Sections 8.1.2 and 8.2.2 respectively.

The Applicant's Position:
Overall, the efficacy, safety, and PK data support the proposed dosing regimen for the mCRC indication. The recommended dosing regimen for EC when combined with mFOLFOX6 is encorafenib 300 mg QD and cetuximab 500 mg/m^2 Q2W.

The FDA's Assessment:
See Section 6 for FDA assessment of dose-response relationship and data to support the proposed dosing regimen.

Durability of Response

Data:
Duration of response was a secondary study endpoint and is summarized in Section 8.1.2.

The Applicant's Position:
See Applicant's Position Key Secondary Efficacy Endpoint Analysis.

The FDA's Assessment:
See the FDA's assessment of the key secondary efficacy endpoints.

Persistence of Effect

Data:
See Efficacy Results-Secondary and other relevant endpoints.

The Applicant's Position:
See Applicant's Position Key Secondary Efficacy Endpoint Analysis.

The FDA's Assessment:
See the FDA's assessment of the key secondary efficacy endpoints.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Data:
Data not presented in this report.

The Applicant's Position:
Data not presented in this report.

The FDA's Assessment:
Not applicable

Additional Analyses Conducted on the Individual Trial

Data:
Not Applicable.

The Applicant's Position:
Not Applicable.

The FDA's Assessment:
Not applicable

8.1.3. **Integrated Review of Effectiveness**

The FDA's Assessment:
See the FDA's assessment in section 8.1.5.

8.1.4. **Assessment of Efficacy Across Trials**
This application is supported by a single trial; thus, this section is not applicable to this review.

8.1.5. **Integrated Assessment of Effectiveness**
The Applicant's Position:

- Efficacy data from the randomized Phase 3 portion of BREAKWATER demonstrated a clinically meaningful and statistically significant benefit of treatment with the EC + mFOLFOX6 regimen versus standard of care for first-line participants with *BRAF* V600E-mutant mCRC.
  - The study met its primary objective of demonstrating clinically and statistically significant improvement in confirmed ORR by BICR for the EC + mFOLFOX6 Arm compared to the Control Arm (60.9% [95% CI: 51.6, 69.5] vs 40.0% [95% CI: 31.3, 49.3], respectively; odds ratio = 2.443 [95% CI: 1.348, 4.380] [99.8% CI: 0.989, 6.089], 1-sided $p < 0.0008$; 1-sided alpha=0.001).

- BOR of CR or PR by BICR was observed in 3 (2.7%) and 64 (58.2%) participants in the EC + mFOLFOX6 Arm and 2 (1.8%) and 42 (38.2%) participants in the Control Arm, respectively.
- The robustness of the ORR results was confirmed by several pre-specified sensitivity and subgroup analyses, which yielded results consistent with the primary analysis.
- Objective responses by BICR in the EC + mFOLFOX6 Arm were rapid, durable, and clinically meaningful compared with the Control Arm.
- The median DOR by BICR for responding participants in the EC + mFOLFOX6 Arm was 13.9 months (95% CI: 8.5, NE) and in the Control Arm was 11.1 months (95% CI: 6.7, 12.7), with 37.3% and 11.4% of the responding participants still ongoing without subsequent progression or death, respectively. Of the objective responders, 68.7% EC + mFOLFOX6 Arm and 34.1% Control Arm had an objective response by BICR lasting ≥6 months, and 22.4% and 11.4% had responses, respectively, lasting ≥12 months.
- The median TTR by BICR in the EC + mFOLFOX6 Arm was 7.1 weeks (range: 5.7, 53.7) and in the Control Arm was 7.3 weeks (range: 5.4, 48.0), both corresponding to the approximate time of the first on-treatment tumor scan.
- The efficacy in the Control Arm (ORR 40%) is consistent with the data from a recent retrospective meta-analysis based on 10 randomized controlled trials in the first-line setting in patients with *BRAF V600E*-mutant mCRC [ORR 35%; (Cohen et al, 2021)], suggesting that the superiority of the EC + mFOLFOX6 Arm was demonstrated against a valid standard of care.
- OS was not mature at the data cutoff date, with 40 (16.9%) deaths in the EC + mFOLFOX6 Arm and 72 (29.6%) deaths in the Control Arm, but no detrimental effect was observed with EC + mFOLFOX6 vs the control therapy (HR 0.47, 95% CI: 0.318, 0.691).

The FDA's Assessment:

The analysis of effectiveness of encorafenib in combination with cetuximab and mFOLFOX6 was based on data submitted from the first 110 patients each enrolled in the EC + mFOLFOX6 and control arm in the BREAKWATER trial. The FDA agrees with the Applicant's position that the study demonstrated a clinically meaningful and statistically significant improvement in confirmed ORR by BICR for the EC + mFOLFOX6 Arm compared to the Control Arm (60.9% [95% CI: 51.6, 69.5] vs 40.0% [95% CI: 31.3, 49.3], respectively). The responses are durable (median DOR by BICR: 13.9 months [95% CI: 8.5, NE] in the EC+mFOLFOX6 Arm). OS was not mature with a positive trend observed (HR=0.47 [95% CI: 0.32, 0.69]).

The FDA also conducted an analysis of the EC alone Arm, which had been discontinued prior to the PCD analysis of BICR-ORR. Based on the response data for the EC alone Arm in 158 patients, the ORR was 46% [95% CI: 38, 53]. Although results from the EC Arm cannot be directly compared to either the EC + mFOLFOX6 or Control Arms, the responses support the conclusion that both EC and mFOLFOX6 are necessary for the (higher) observed treatment effect in the BREAKWATER trial. EC + mFOLFOX6 appears reasonably likely to be substantially better than available therapy. In BREAKWATER, available therapy consisted of investigator's choice of different chemotherapy regimens. Although about 23% of patients

received the more active regimen (FOLFOXIRI), use of FOLFOXIRI (or more commonly mFOLFIRNOX in the US) is limited to select fit patients, and therefore the overall comparator arm that included doublet chemotherapy was acceptable (as this regimen is commonly used in practice).

The results support granting accelerated approval to this application.

A PMR will be issued to provide the results of the completed PFS analysis from the BREAKWATER trial to verify the clinical benefit of EC + mFOLFOX6. The BREAKWATER trial is fully enrolled, and the PFS analysis is anticipated in May of 2025.

8.2. **Review of Safety**

The Applicant's Position:

The safety analyses comprise a total of 258 participants treated with EC + mFOLFOX6 (231 from Phase 3 and 27 from the SLI). Safety data from the Phase 3 portion of BREAKWATER, with a data cutoff of 22 December 2023, presented in Section 8.2.4, serve as the primary safety analyses that support the use of the combination of EC + mFOLFOX6 in patients with *BRAF* V600E-mutant mCRC. The safety assessment of the EC + mFOLFOX6 regimen is based primarily on the Phase 3 EC + mFOLFOX6 Arm. Supportive safety data from the SLI portion of BREAKWATER, with a data cutoff of 22 December 2023, are included for AESIs and ADRs only.

Pooled analyses for the safety data from the Phase 3 and SLI are provided for EC + mFOLFOX6 for AESIs and ADRs only. Safety data for the EC + mFOLFOX6 Cohort of the SLI are pooled with the corresponding EC + mFOLFOX6 Arm of Phase 3 and are presented side-by-side and as a pooled population (N=258) (presented in Section 8.2.11). Data other than AESIs and ADRs from the SLI portion of the study are not included in this document but are provided in the CSR. In addition, the Phase 3 portion of the study initially included the EC Arm into which enrollment was discontinued with Protocol Amendment 5; thus, the EC Arm is included in relevant summary tables, but in-text discussions of the EC Arm are only presented in the CSR.

In Phase 3, safety was a secondary objective of the study and the safety analyses included summaries of AEs, SAEs, deaths, AEs leading to permanent treatment discontinuations, AEs leading to dose reductions, AEs leading to dose interruptions, AESIs, clinical laboratory evaluations, vital signs, and ECGs. Safety analyses are summarized for all participants in Phase 3 who were evaluable for safety (ie, received at least 1 dose of study intervention) with the in-text discussion mainly focusing on the safety and tolerability of the EC + mFOLFOX6 combination.

The overall safety population is considered appropriate for the detection and characterization of AEs and to provide guidance on management of AEs.

Data presented in this submission allowed for an informed assessment of the safety profile of the EC + mFOLFOX6 combination and an evaluation of the overall benefit-risk in participants with *BRAF* V600E-mutant mCRC. The overall safety profile of the EC + mFOLFOX6 combination was generally consistent with the known safety profiles of the individual agents within the combination. No new safety signals were identified.

The FDA's Assessment:
The primary basis of the FDA's safety review was data provided from the Phase 3 portion of the BREAKWATER (C4221015) trial with a data cutoff date of December 22, 2023. The assessment of the adverse events focused on the primary safety population, which includes all patients who received at least one dose of the study intervention in Phase 3 of the trial either in EC + mFOLFOX6 arm (n=231) or in the Control Arm (n=228).

8.2.1. **Safety Review Approach**

The Applicant's Position:
The safety data presented in this submission are a comprehensive analysis of safety data relevant to the use of the EC + mFOLFOX6 combination in the intended treatment population of patients with *BRAF* V600E-mutant mCRC. Safety analyses were performed on all participants who received at least 1 dose of study intervention:

- The Phase 3 Safety Set included 231 participants EC + mFOLFOX6 Arm and 228 participants Control Arm.
- The SLI Safety Set included 27 participants EC + mFOLFOX6 Cohort.
- The EC + mFOLFOX6 POOLED Set (N=258) include all participants treated in the EC + mFOLFOX6 Arm of Phase 3 and all participants treated in the EC + mFOLFOX6 Cohort of the SLI. The EC + mFOLFOX6 POOLED Set is used for AESIs and ADRs only.

The following safety data are being provided in this submission: AEs, SAEs, deaths, AEs leading to permanent treatment discontinuations, AEs leading to dose reductions, AEs leading to dose interruptions, AESIs, clinical laboratory evaluations, vital signs, and ECGs.

The focus of the safety review, based on the CSR, CRFs, and safety narratives, was to ascertain if there are any new clinically important safety issues or changes in the known safety profile of encorafenib when combined with cetuximab and mFOLFOX6 that would need to be included in the product label.

The safety review approach implemented was appropriate for the patient population studied, and consistent with that evaluated in previous submissions of encorafenib.

The FDA's Assessment:
FDA did not confirm or perform safety analyses of the data provided for EC Arm and FDA's review was centered on the EC + mFOLFOX6 combination arm as the proposed indication of this application.

Pre-defined by the Applicant adverse events of special interest (AESI) were analyzed based on data from patients treated with EC + mFOLFOX6 regimen in the Phase 3 portion of the BREAKWATER trial and pooled safety data, which included patients treated with EC + mFOLFOX6 regimen in the Safety Lead-In (SLI) portion and Phase 3.

8.2.2. **Review of the Safety Database**

Overall Exposure

Data:
The median duration of exposure to study treatment was 28.1 weeks (range: 1.3 to 107.4 weeks) in the EC + mFOLFOX6 Arm (N=231) and 20.4 weeks (range: 1.1 to 98.3 weeks) in the Control

Arm (N=228), with 58.1%, and 33.7% of participants, respectively, still receiving study treatment at the time of the data cutoff.

- 13.0% EC + mFOLFOX6 Arm and 3.5% Control Arm received ≥60 weeks of study treatment.

High median relative dose intensity was achieved for most study intervention components in the EC + mFOLFOX6 Arm, indicating that the toxicities were manageable.

- Median relative dose intensity in the EC + mFOLFOX6 Arm was encorafenib 91.7% (range: 3.0% to 100.7%), cetuximab 94.2% (range: 38.4% to 199.4%), fluorouracil 82.7% (range: 46.6% to 102.8%), leucovorin 94.1% (range: 47.0% to 199.4%), and oxaliplatin 84.2% (range: 41.6% to 201.9%).

The Applicant's Position:
Exposure to encorafenib, cetuximab, and mFOLFOX6 presented in this submission provided sufficient safety data for assessing the safety profile of the EC + mFOLFOX6 combination in participants with *BRAF* V600E-mutant mCRC.

The FDA's Assessment:
FDA analyzed exposure utilizing the observed duration of the treatment and the median relative dose intensity for each agent comprising the EC + mFOLFOX6 arm and for each agent comprising the Control arm presented in Table 17. Summary Exposure to the Treatment

The observed median duration of treatment was slightly longer in the investigational arm compared to the control. Out of 231 patients who received encorafenib in the EC + mFOLFOX6 arm, 54% were exposed for 6 months or longer and 18% were exposed for one year or longer. The treatment exposure was considered adequate for the safety analysis.
Additionally, the observed median relative dose intensity for most components of the EC + mFOLFOX6 arm was greater than 85%, indicating strong patient adherence to the dosing regimen.

Table 17. Summary Exposure to the Treatment

	EC + mFOLFOX6 Arm (n=231)				
	Encorafenib	**Cetuximab**	**Fluorouracil**	**Leucovorin**	**Oxaliplatin**
Number of patients	229	230	231	231	231
Median duration of exposure, weeks	27.6 (0.4 - 107.4)	27.1 (1.3 - 107.4)	24.9 (1.3 - 107.4)	24.9 (1.3 - 107.4)	18.9 (1.3 - 76.6)
Median Relative Dose Intensity, %	91.7	94.2	82.7	94.1	84.2

	Control Arm (n=228)					
	Fluorouracil	Leucovorin	Irinotecan	Oxaliplatin	Capecitabine	Bevacizumab
Number of patients	181	179	66	228	47	195
Median duration of exposure, weeks	20.4 (1.3 - 96.6)	20.1 (1.3 - 96.6)	21.4 (2.0 - 96.6)	16.7 (1.1 - 98.3)	17.0 (1.1 - 98.1)	20.0 (1.1 - 98.3)
Median Relative Dose Intensity, %	90.3	98.8	87.2	92.4	68.6	99.3

Relevant characteristics of the safety population:
Data: Not applicable.
The Applicant's Position:
The eligibility criteria in BREAKWATER were clinically relevant for the target population of patients with *BRAF* V600E-mutant mCRC. Demographic and baseline disease characteristics were generally well-balanced between the 2 treatment arms.

There were no notable observations in demographics, disease and baseline characteristics, medical conditions, or concomitant medications for BREAKWATER that would likely impact the interpretation of the safety results.

The FDA's Assessment:
FDA agrees with the Applicant's characterization of the eligibility criteria for the target population. The treatment arms are representative of the baseline characteristics of the intended population in terms of sex, race, and ethnicity. Although, the U.S. population represents only 5% of the overall study population, and EC+FOLFOX arm includes fewer patients aged >65 compared to the control arm (36% vs. 43% respectively), these factors are not expected to impact the safety analysis results.

Adequacy of the safety database:
Data:
The safety analyses comprise a total of 258 participants treated with EC + mFOLFOX6 (231 from Phase 3 and 27 from the SLI).

- In the 231 participants who were treated with EC + mFOLFOX6 in Phase 3, the median duration of treatment was 28.1 weeks (range: 1.3 to 107.4 weeks).
- In the 27 participants who were treated with EC + mFOLFOX6 in the SLI, the median duration of treatment was 37.9 weeks (range: 4.0 to 145.4 weeks).

The Applicant's Position:
The design of BREAKWATER including the frequency and assessments collected, the overall size of the safety data set, and the extent of exposure to the EC + mFOLFOX6 combination at the proposed dose level are sufficient to characterize the safety of the regimen and permit a

rigorous assessment of the combination as treatment for the proposed indication of patients with *BRAF* V600E-mutant mCRC.

The pooling of AESI and ADR data from participants who received EC + mFOLFOX6 in the Phase 3 and SLI portions of BREAKWATER enables summarization of key safety data in the greatest possible number of participants, allowing for frequency estimates for rarer events and detection of less common potential ADRs.

The patient population in BREAKWATER with respect to age, [redacted] and other demographic, disease and baseline characteristics is consistent with that expected for the proposed indication, enabling these results to be generalized to patients with *BRAF* V600E-mutant mCRC (Section 8.1.2 Demographics). The racial distribution reflects the regions in which the study was conducted.

The FDA's Assessment:
The size of the safety population, level of exposure to the investigational treatment are adequate to evaluate the safety of the EC + mFOLFOX6 combination regimen in patients with BRAFV600E-mutant mCRC. Safety datasets are expected to be generalizable, considering their adequacy and overall representative demographic characteristics. Additionally, there is experience with the use of encorafenib in combination with cetuximab (without chemotherapy in the later line CRC setting).

8.2.3. **Adequacy of Applicant's Clinical Safety Assessments**
Issues Regarding Data Integrity and Submission Quality
The Applicant's Position:
All reasonably applicable clinical evaluations were conducted to assess the safety of the EC + mFOLFOX6 combination, including during the COVID-19 pandemic. During the study, these evaluations were performed at sufficiently frequent time intervals, in accordance with standard clinical practice. In BREAKWATER, protocol deviations were deemed to have a negligible impact on the safety results of the study.

The Sponsor has a comprehensive quality management system in place for monitoring safety data quality across all clinical trials. Quality management methods include site inspections, safety data review by qualified experts, management of data quality (site collection, site-to-Sponsor data transmission, data analysis and data summarization), and management of regulatory document quality. No issues were identified regarding data integrity or submission quality that impacted the clinical safety review.

The FDA's Assessment:No issues were identified regarding data integrity. The sNDA submission was of adequate quality to allow for review of the safety data provided to support the application Additionally, refer to Section 4.1 regarding clinical site inspection process.

Categorization of Adverse Event
The Applicant's Position:
AEs were collected as specified in the BREAKWATER study protocol. AEs were coded using MedDRA v26.1 and graded according to NCI CTCAE Version 4.03. Safety analyses were

summarized by treatment arm for Phase 3. The analyses described in this submission were based on TEAEs, unless otherwise specified, and are denoted as "AEs" in this document.

TEAEs were defined as AEs with onset date during the on-treatment period. For BREAKWATER, the on-treatment period was defined as the time from the first dose of study treatment to the last dose of study treatment +28 days, or the earliest start date of subsequent anticancer systemic therapy minus 1 day, whichever occurred first.

Seriousness, relationship to study drug, toxicity grade, action taken (interruption, reduction, and permanent discontinuation), and clinical outcome of AEs were as reported by the Investigator.

AEs were summarized by presenting the number and percentage of participants having at least 1 AE and having at least 1 AE by SOC and/or PT, maximum severity grade (based on CTCAE grades), and relationship to study drug.

Actions taken with study drug(s) (ie, dose reductions, dose interruptions, and permanent discontinuation of study drug[s]) as a result of AEs were summarized.

AESIs for encorafenib were prospectively defined over the course of the study as AEs for which there was a specific clinical interest in connection with encorafenib treatment (based on signals observed from previous studies in the clinical development program involving encorafenib and/or they are known toxicities of other BRAFis) or for which there is potential overlap with the safety profile of cetuximab and/or chemotherapy. The defined AESIs represent broad search strategies to identify potentially relevant AEs that include groupings of MedDRA PTs that are similar in nature, although not identical. AESI groupings are presented using capital letters in the sections that describe AESIs. AESIs were coded using MedDRA v26.1. The following AESI groupings for encorafenib were defined: CUTANEOUS NON-SQUAMOUS CELL CARCINOMA, FACIAL PARESIS, HEPATIC FAILURE, MYELOSUPPRESSION, and QT PROLONGATION.

Clinical laboratory test results were graded using NCI CTCAE v4.03 or were classified based on normal range if not evaluated per CTCAE.

The FDA's Assessment:

Generally, FDA agrees with the Applicant's position regarding the definition, categorization, coding, and collection of the adverse events (AEs). FDA safety analysis of treatment-emergent adverse events (TEAEs) was based on MedDRA version 26.1 Preferred Terms. Only the worst grade for each TEAE and laboratory abnormality was included for each patient. For the purpose of the FDA's safety review, the incidence of AEs was analyzed regardless of investigator attribution.

The incidence of AEs and laboratory abnormalities were calculated as a percentage of patients experiencing at least one AE by preferred term (PT), or only one within grouped term (GT), if applicable, relative to the total number of patients in the respective treatment arm.

In line with FDA Oncology review practices, highly related and clinically relevant terms were grouped together. Following adverse events were analyzed as a GTs:

- GT 'Neuropathy Peripheral' includes the PTs: cold dysaesthesia, neuropathy peripheral,

peripheral sensory neuropathy, paraesthesia, dysaesthesia, hypoaesthesia, polyneuropathy, peripheral motor neuropathy, and neuralgia.
- GT 'Abdominal Pain' includes PTs: abdominal pain, abdominal pain upper, abdominal pain lower, hepatic pain, abdominal discomfort, epigastric discomfort, and abdominal tenderness.
- GT 'Stomatitis' includes PTs: mucosal inflammation, stomatitis, mouth ulceration, pharyngeal inflammation, aphthous ulcer, cheilitis, and glossitis.
- GT 'Fatigue' includes PTs: fatigue, asthenia.
- GT 'Rash' includes PTs : eyelid rash, nodular rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular.
- GT 'Dermatitis acneiform' includes PTs: acne, dermatitis acneiform.
- GT 'Dry skin' includes PTs : dry skin, skin fissures, xeroderma, xerosis.
- GT 'Myopathy' includes PTs: myalgia, musculoskeletal chest pain, musculoskeletal discomfort, muscle contracture, muscle disorder, muscle spasms, muscular weakness, myositis.
- GT 'Arthralgia' includes PTs: arthralgia, joint stiffness, musculoskeletal pain.
- GT 'Hemorrhage' includes PTs: anal haemorrhage, conjunctival haemorrhage, epistaxis, gastrointestinal haemorrhage, gingival bleeding, haematochezia, haematuria, haemoptysis, haemorrhoidal haemorrhage, heavy menstrual bleeding, intermenstrual bleeding, lower gastrointestinal haemorrhage, melaena, occult blood, orbital haematoma, rectal haemorrhage, stoma site haemorrhage, subdural haematoma, tumour haemorrhage, umbilical haemorrhage, upper gastrointestinal haemorrhage, vaginal haemorrhage
- GT 'Vomiting' includes PTs: retching, and vomiting

FDA agrees with the applicant's strategy for defining and grouping of the adverse event of special interest (AESIs) for encorafenib that are clinically relevant and have overlapping potential.

Routine Clinical Tests

The Applicant's Position:

All clinical tests were routine safety assessments in the study population and comprehensive and consistent with the clinical guidelines for patients with mCRC. These assessments were appropriate for participants with mCRC and were also based on the known safety profiles of the study interventions included in the trial.

Per protocol, hematology and coagulation, chemistries, urinalysis tests, vital signs, and ECG assessments were collected at the time points described in the Schedule of Activities of the BREAKWATER study protocol. Laboratory test samples were analyzed at a central laboratory. Local site laboratories were permitted to be utilized, in addition to the central laboratory, if more rapid results were required for treatment decisions or for participant safety.

The FDA's Assessment:

FDA agrees with the Applicant's description of clinical and laboratory monitoring of patients for adverse reactions. The safety assessments and their schedule in the study were appropriate for

evaluating potential adverse events of the study treatment in patients with mCRC. Using local laboratory test results for time-sensitive safety assessments is acceptable, provided that central laboratory validation is available.

8.2.4. **Safety Results**

Deaths

Data:

Deaths during the study occurred in 16.5% EC + mFOLFOX6 Arm and 30.3% Control Arm of the Safety Set (Table 18).

- Deaths ≤28 days after last dose of study treatment were reported for 4.3% EC + mFOLFOX6 Arm and 4.4% Control Arm; most deaths ≤28 days after last dose of study treatment were due to the disease under study.
  - Deaths ≤28 days after last dose of study treatment due to disease under study occurred in 3.9% EC + mFOLFOX6 Arm and 3.1% Control Arm.
  - Deaths ≤28 days after last dose of study treatment due to events other than disease under study in the EC + mFOLFOX6 Arm were GI perforation (0.4%); and in the Control Arm were cardiac arrest, septic shock, and study treatment toxicity (0.4% each).
- All-causality Grade 5 AEs occurred in 4.3% EC + mFOLFOX6 Arm and 4.4% Control Arm.
  - All causality Grade 5 AEs in the EC + mFOLFOX6 Arm were disease progression (2.6%), intestinal obstruction (0.9%), and GI perforation and large intestinal perforation (0.4% each); and in the Control Arm were general physical health deterioration (0.9%), and abdominal sepsis, cardiac arrest, colorectal cancer, dyspnea, large intestinal perforation, pneumonia, respiratory failure, sepsis, and septic shock (0.4% each).
  - No Grade 5 treatment-related AEs were reported in the EC + mFOLFOX6 Arm. One participant (0.4%) in the Control Arm had a treatment-related Grade 5 AE of sepsis.

Table 18. Applicant - Summary of Deaths - Phase 3 Safety Set (Protocol C4221015)

	EC (N=154) n (%)	EC+mFOLFOX6 (N=231) n (%)	Control (N=228) n (%)
Death	43 (27.9)	38 (16.5)	69 (30.3)
Cause of Death			
Disease Under Study	40 (26.0)	35 (15.2)	60 (26.3)
Acute Myelocytic Leukemia	1 (0.6)	0 (0.0)	0 (0.0)
Cardiac Arrest	0 (0.0)	0 (0.0)	1 (0.4)
Commit Suicide	1 (0.6)	0 (0.0)	0 (0.0)
Disease Progression	0 (0.0)	0 (0.0)	1 (0.4)
Gastrointestinal Perforation	0 (0.0)	1 (0.4)	0 (0.0)
Immunocheckpoint Inhibitor Associated Myocarditis	1 (0.6)	0 (0.0)	0 (0.0)
Ischemia Cerebrovascular	0 (0.0)	1 (0.4)	0 (0.0)

Table 18. Applicant - Summary of Deaths - Phase 3 Safety Set (Protocol C4221015)

	EC (N=154) n (%)	EC+mFOLFOX6 (N=231) n (%)	Control (N=228) n (%)
Post-Covid Pulmonary Fibrosis	0 (0.0)	1 (0.4)	0 (0.0)
Progression Disease	0 (0.0)	0 (0.0)	1 (0.4)
Septic Shock	0 (0.0)	0 (0.0)	1 (0.4)
Study Treatment Toxicity	0 (0.0)	0 (0.0)	2 (0.9)
Unknown	0 (0.0)	0 (0.0)	3 (1.3)
Deaths Within 28 Days After Last Dose of Study Treatment	3 (1.9)	10 (4.3)	10 (4.4)
Cause of Death			
Disease Under Study	3 (1.9)	9 (3.9)	7 (3.1)
Cardiac Arrest	0 (0.0)	0 (0.0)	1 (0.4)
Gastrointestinal Perforation	0 (0.0)	1 (0.4)	0 (0.0)
Septic Shock	0 (0.0)	0 (0.0)	1 (0.4)
Study Treatment Toxicity	0 (0.0)	0 (0.0)	1 (0.4)
Deaths Within 30 Days After First Dose of Study Treatment	0 (0.0)	1 (0.4)	3 (1.3)
Cause of Death			
Disease Under Study	0 (0.0)	1 (0.4)	2 (0.9)
Septic Shock	0 (0.0)	0 (0.0)	1 (0.4)

The denominator to calculate percentages is N, the number of participants in the Safety Analysis Set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:51) Source Data: adsl Table Generation: 15APR2024 (19:20) (Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR PCD/C4221015_PH3_20240319_Unblinded/adsl_s013_p3
Table 14.3.2.2.1.1 encorafenib is for Pfizer internal use.

The Applicant's Position:
Deaths ≤28 days after last study treatment dose were reported at similar frequencies in the EC + mFOLFOX6 Arm and Control Arm, and were mostly due to disease under study. No Grade 5 treatment-related AEs were reported in the EC + mFOLFOX6 Arm. One participant (0.4%) in the Control Arm had a treatment-related Grade 5 AE of sepsis.

The FDA's Assessment:
The analysis of all deaths during the study was consistent with the Applicant's findings, with 16 % (n=38) of deaths occurred in the EC + mFOLFOX6 Arm and 30.3% (n=69) in the Control Arm reported and disease progression being the primary cause of deaths in the EC + FOLFOX arm.

FDA's analysis of deaths due to adverse events was conducted based on the review of fatal outcomes occurred during on-treatment period defined as the time from the first dose of the study treatment and up to 30 days after the last dose Ten adverse events with fatal outcomes

were reported in the EC + mFOLFOX Arm. Six of these patients died due to disease progression, four patients died due to intestinal obstruction and gastrointestinal (GI) perforation, with two cases of each. In the Control Arm large intestinal perforation was reported as cause of death in one patient. Table 19

The data analysis and relevant patient narratives for deaths due to AEs were reviewed across the EC, EC + mFOLFOX6, and Control Arms. The review team agreed with the determination of disease progression as the cause of death in six of ten cases in the EC + FOLFOX arm. For the remaining four cases the narratives summarized in Table 20. Based on the provided information in narratives, a contribution of the investigational regimen to the fatal outcome cannot be definitively ruled out. FDA agrees with the narrative for the intestinal obstruction event is likely due to disease progression and can be removed. It is FDA's opinion that the potential for gastrointestinal perforation while on this regimen (even if indirectly due to study treatment effects on tumor) is a clinically serious and significant risk that should be including in drug labeling.

Additionally, upon reviewing the narratives of deaths in patients who experienced adverse events in the control arm, the reviewer noted that in six cases, where the applicant attributed the deaths to general physical health deterioration, large intestinal perforation, abdominal sepsis, pneumonia and colorectal cancer, there was also evidence of disease progression in these patients.

Table 19. Summary of Deaths due to AE

	EC N = 154 N (%)	EC+MFOLFOX6 N = 231 N (%)	CONTROL N = 228 N (%)
Death due to AEs	**2 (1.3)**	**10 (4.3%)**	**10 (4.4%)**
Disease Progression	2 (1.3)	6 (2.6%)	0 (0.0%)
Intestinal Obstruction	0 (0.0)	2 (0.9%)	0 (0.0%)
Gastrointestinal Perforation	0 (0.0)	1 (0.4%)	0 (0.0%)
Large Intestine Perforation	0 (0.0)	1 (0.4%)	1 (0.4%)
Abdominal Sepsis	0 (0.0)	0 (0.0%)	1 (0.4%)
Cardiac Arrest	0 (0.0)	0 (0.0%)	1 (0.4%)
Colorectal Cancer	0 (0.0)	0 (0.0%)	1 (0.4%)
Dyspnoea	0 (0.0)	0 (0.0%)	1 (0.4%)
General Physical Health Deterioration	0 (0.0)	0 (0.0%)	2 (0.9%)
Pneumonia	0 (0.0)	0 (0.0%)	1 (0.4%)
Respiratory Failure	0 (0.0)	0 (0.0%)	1 (0.4%)
Sepsis	0 (0.0)	0 (0.0%)	1 (0.4%)
Septic Shock	0 (0.0)	0 (0.0%)	1 (0.4%)

Table 20. Summary of the Narratives of Deaths Due to Intestinal Perforation and Obstruction

SAE Gr5 reported	Reported cause of death	Summary of narratives of deaths and comments
Intestinal obstruction	Acute Intestinal obstruction, intoxication, bowel perforation, ascending colon cancer	(b) (6) *A 71-year-old female patient started study treatment on* (b) (6) *On* (b) (6) *patient was hospitalized due to intestinal obstruction and died on* (b) (6) *No confirmatory evidence (biopsy, CT, etc.) of progression provided. Reported cause of death: "acute intestinal obstruction," "intoxication," "bowel perforation," "ascending colon cancer."*
GI perforation	Diverticula of colon	(b) (6) *A 73-year-old female started study treatment on* (b) (6) *Hospitalized on* (b) (6) *due to abdominal pain and died the same day due to Gastrointestinal Perforation. Autopsy CT showed free air (pelvic predominance) and ascites accumulation (right-sided predominance). A causal relationship with the study treatment could not be conclusively excluded.*
Intestinal obstruction	Intestinal obstruction	(b) (6) *A 65-year-old male received study treatment from* (b) (6) *On* (b) (6) *the patient was hospitalized due to intestinal obstruction and died on the same day. CT showed colonic mass, invasion of right iliopsoas and psoas. Local obstruction secondary to proximal cecum, reexamination recommended; multiple pelvic exudations, effusion, peritoneal thickening, considering inflammation. A causal relationship could not be excluded.*
Large-intestine perforation	Disease progression Colonic perforation	(b) (6) *A 66-year-old female patient started study treatment with EC+FOLFOX on* (b) (6)*. On* (b) (6) *she experienced large-intestine perforation with fatal outcome. Previous SAE of hospitalization due to peritonitis and sepsis reported on* (b) (6) (b) (6) *mentioned "hepatic and possible peritoneal metastasis"; imaging had been consistent with "ileus." Presented imaging results and clinical course do not conclusively exclude the contribution of the study treatment.*

Serious Adverse Events

Data:

All-causality SAEs occurred in a similar percentage of participants in the EC + mFOLFOX6 Arm (37.7%) and Control Arm (34.6%).

- The most frequent (≥3% of participants) all-causality SAEs by PT in the EC + mFOLFOX6 Arm were disease progression, intestinal obstruction, and pyrexia (3.5% each); and in the Control Arm were febrile neutropenia (3.5%) and abdominal pain (3.1%).
- Treatment-related SAEs occurred in 18.2% EC + mFOLFOX6 Arm and 19.3% Control Arm.

The Applicant's Position:

SAEs were generally consistent with the known safety profiles of each agent or associated with underlying disease/intercurrent medical conditions; no new safety signals were identified.

The FDA's Assessment:

FDA generally agrees with the incidence rates of the SAEs reported in applicant`s analysis. For the purpose of the review of safety, FDA did not consider disease progression as a toxicity associated with the study treatment, thus it was excluded from the description of SAEs.

The most frequently occurring SAEs in the EC + mFOLFOX6 arm were intestinal obstruction and pyrexia, each reported in 3.5% of patients. Upon review of the narratives of patients who experienced SAEs, the cases of pyrexia and intestinal obstruction may represent an intercurrent medical conditions influenced by the patient's underlying malignancy and potentially related to the disease itself or complications of the patient's medical comorbidities.

In the Control arm, the most frequently reported SAEs were consistent with those expected from chemotherapy, such as febrile neutropenia (3.5%) and abdominal pain (3.1%).

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

All-causality AEs associated with permanent discontinuation are summarized in Table 21.

Table 21. Applicant — All-Causality AEs Associated with Permanent Discontinuation - Phase 3 Safety Set (Protocol C4221015) – (Data Cutoff Date: 22Dec2023)

Study Intervention	AEs associated with permanent discontinuation
Any Study Intervention (ie, encorafenib, and/or cetuximab, and/or all components of other study intervention)	All-causality AEs associated with permanent discontinuation of any study intervention occurred in 20.8% EC + mFOLFOX6 Arm and 14.9% Control Arm; the most frequent (≥1% of participants) in the EC + mFOLFOX6 Arm were asthenia, disease progression, and lipase increased (1.7% each), and anemia, nausea, and neutrophil count decreased (1.3% each); and in the Control Arm were intestinal obstruction and general physical health deterioration (1.3% each).
Encorafenib	All-causality AEs associated with permanent discontinuation of encorafenib occurred in 11.7% EC + mFOLFOX6 Arm; the most frequent (≥1% of participants) in the EC + mFOLFOX6 Arm were disease progression and lipase increased (1.7% each).
Cetuximab	All-causality AEs associated with permanent discontinuation of cetuximab occurred in 13.0% EC + mFOLFOX6 Arm; the most frequent (≥1% of participants) in the EC + mFOLFOX6 Arm were disease progression and lipase increased (1.7% each).
Other Study Intervention (ie, all components; includes: irinotecan, oxaliplatin, leucovorin or levo-leucovorin, fluorouracil (bolus or infusion), capecitabine, and bevacizumab [as appropriate for the treatment group])	All-causality AEs associated with permanent discontinuation of other study intervention occurred in 15.6% EC + mFOLFOX6 Arm and 14.9% Control Arm; the most frequent (≥1% of participants) in the EC + mFOLFOX6 Arm were disease progression (1.7%) and asthenia (1.3%); and in the Control Arm were intestinal obstruction and general physical health deterioration (1.3% each).

The Applicant's Position:

The most frequently reported AEs leading to permanent treatment discontinuation were generally consistent with the known safety profiles of each agent or associated with underlying disease. The addition of EC to chemotherapy was not associated with significant increase in chemotherapy discontinuation.

The FDA's Assessment:
Based on FDA analysis, the AEs, leading to treatment discontinuation of any study intervention were reported in 20.8% of patients in the EC + mFOLFOX6 rarm, and in 14.9% in the control arm. AEs resulted in permanent discontinuation of encorafenib in 11.7% of patients with the most frequently reported reason of discontinuation of lipase increased, which occurred in 1.7% of patients (n=4). AEs which resulted in treatment discontinuation in the Control Arm in 1.3% of patients each (n=3) were intestinal obstruction and general physical health deterioration.

FDA agrees that addition of the EC to FOLFOX regimen did not lead to an unacceptable increased rate of therapy discontinuation.

Dose Interruption, Delays and/or Reductions Due to Adverse Effects
Data:
All-causality AEs associated with dose interruptions or dose reductions are summarized in Table 22.

Table 22. Applicant — AEs Associated with Dose Interruption or Dose Reduction - Phase 3 Safety Set (Protocol C4221015) – (Data Cutoff Date: 22Dec2023)

Study Intervention	AEs associated with dose interruption	AEs associated with dose reduction
Any Study Intervention	All-causality AEs associated with dose interruption of any study intervention occurred in 84.8% EC + mFOLFOX6 Arm and 64.0% Control Arm; the most frequent (≥10% of participants) in the EC + mFOLFOX6 Arm were neutrophil count decreased (16.9%), neutropenia and pyrexia (13.0% each), and neuropathy peripheral (10.0%); and in the Control Arm was neutrophil count decreased (12.3%).	All-causality AEs associated with dose reduction of any study intervention occurred in 61.0% EC + mFOLFOX6 Arm and 47.8% Control Arm; the most frequent (≥5% of participants) in the EC + mFOLFOX6 Arm were neutropenia and neutrophil count decreased (10.0% each), neuropathy peripheral (5.6%), and neurotoxicity and platelet count decreased (5.2% each); and in the Control Arm were neutropenia (9.6%), neutrophil count decreased (9.2%), and neuropathy peripheral and peripheral sensory neuropathy (5.3% each).
Encorafenib	All-causality AEs associated with dose interruption of encorafenib occurred in 56.7% EC + mFOLFOX6 Arm; the most frequent (≥5% of participants) in the EC + mFOLFOX6 Arm were neutrophil count decreased and pyrexia (6.9% each), anemia (6.5%), and neutropenia (5.6%).	All-causality AEs associated with dose reduction of encorafenib occurred in 22.1% EC + mFOLFOX6 Arm; the most frequent (≥2% of participants) in the EC + mFOLFOX6 Arm were lipase increased (2.6%), and nausea and vomiting (2.2% each).
Cetuximab	All-causality AEs associated with dose interruption of cetuximab occurred in 58.4% EC + mFOLFOX6 Arm; the most frequent (≥5% of participants) in the EC + mFOLFOX6 Arm were	All-causality AEs associated with dose reduction of cetuximab occurred in 6.1% EC + mFOLFOX6 Arm; the most frequent (≥2% of participants) in the EC

Table 22. Applicant — AEs Associated with Dose Interruption or Dose Reduction - Phase 3 Safety Set (Protocol C4221015) – (Data Cutoff Date: 22Dec2023)

Study Intervention	AEs associated with dose interruption	AEs associated with dose reduction
	neutrophil count decreased (12.6%), neutropenia (10.4%), and anemia, platelet count decreased, and pyrexia (6.5% each).	+ mFOLFOX6 Arm was weight decreased (2.2%).
Other Study Intervention (includes: irinotecan, oxaliplatin, leucovorin or levo-leucovorin, fluorouracil (bolus or infusion), capecitabine, and bevacizumab [as appropriate for the treatment group])	All-causality AEs associated with dose interruption of other study intervention occurred in 75.8% EC + mFOLFOX6 Arm and 64.0% Control Arm; the most frequent (≥10% of participants) in the EC + mFOLFOX6 Arm were neutrophil count decreased (14.3%), neutropenia (10.8%), and neuropathy peripheral (10.0%); and in the Control Arm was neutrophil count decreased (12.3%).	All-causality AEs associated with dose reduction of other study intervention occurred in 55.8% EC + mFOLFOX6 Arm and 47.8% Control Arm; the most frequent (≥5% of participants) in the EC + mFOLFOX6 Arm were neutropenia and neutrophil count decreased (9.5% each), neuropathy peripheral (5.6%), and platelet count decreased (5.2%); and in the Control Arm were neutropenia (9.6%), neutrophil count decreased (9.2%), and neuropathy peripheral and peripheral sensory neuropathy (5.3% each).

The Applicant's Position:
The most frequently reported AEs leading to dose modifications were generally consistent with the known safety profiles of each agent or associated with underlying disease.

The FDA's Assessment:
FDA agrees with the applicant's analysis of AEs leading to dose modifications. TEAEs resulting in dose interruption and dose reduction of encorafenib occurred in 56.7% and 22.1% of patients, respectively. The primary reason for dose interruption of encorafenib in patients who received treatment with EC + mFOLFOX were neutrophil count decreased (6.9%), pyrexia (6.9%) and anemia (6.5%). The most common reasons for dose reduction of encorafenib were lipase increased, observed in 2.6% of patients and nausea and vomiting (reported in 2.2% of patients each).

Significant Adverse Events

Data:

- All-causality Grade 3 or 4 AEs occurred in 74.0% EC + mFOLFOX6 Arm and 61.0% Control Arm. The more frequent Grade 3 or 4 AEs associated with the EC + mFOLFOX6 regimen was mainly driven by myelosuppressive events (eg, neutrophil count decreased/neutropenia, anemia) and neuropathy, which are expected events associated with the mFOLFOX6 regimen and tend to occur more frequently with longer duration of treatment.

- The most frequent (≥5% of participants) all-causality Grade 3 or 4 AEs in the EC + mFOLFOX6 Arm were neutrophil count decreased (18.2%), lipase increased and neutropenia (14.7% each), anemia (10.8%), neuropathy peripheral (6.9%), and peripheral sensory neuropathy and WBC count decreased (5.6% each); and in the Control Arm were neutrophil count decreased (16.7%), neutropenia (9.2%), and lipase increased (5.3%).
  - All-causality Grade 3 or 4 AEs of lipase increased (14.7% vs 5.3%), neutropenia (14.7% vs 9.2%), and anemia (10.8% vs 3.5%) were reported with higher frequency (≥5% difference) in the EC + mFOLFOX6 Arm than the Control Arm.
  - No all-causality Grade 3 or 4 AEs were reported with lower frequency (≥5% difference) in the EC + mFOLFOX6 Arm than the Control Arm.

The Applicant's Position:
Reported Grade 3 or 4 AEs are generally consistent with the known safety profiles of each agent or associated with underlying disease/intercurrent medical conditions.

No changes to current labeling recommendations, including dose modification guidance, are warranted for any of the events presented in this section based on the new safety information in this submission.

The FDA's Assessment:
Based on the FDA`s safety analysis for significant adverse events, the most frequent Grade 3 or 4 AEs, reported in ≥5% of participants in the EC + mFOLFOX6 arm were neuropathy peripheral (15 %) and fatigue (6%), both reported as grouped terms. In the control arm the most frequently reported Grade 3 or 4 AEs were neuropathy peripheral (6 %) and diarrhea (5%). The FDA's analysis of significant adverse myelosuppressive events was based on the laboratory related findings reported in the laboratory abnormalities section.

Treatment Emergent Adverse Events and Adverse Reactions

Data:
An overview of AEs in Phase 3 is provided in Table 23.

- Almost all participants in both the EC + mFOLFOX6 Arm and Control Arm had at least 1 all-causality AE and at least 1 treatment-related AE.
  - The overall frequencies of participants with all-causality and treatment-related AEs and SAEs, and Grade 5 AEs were generally similar between the EC + mFOLFOX6 Arm and the Control Arm.
  - The overall frequencies of participants with all-causality and treatment-related Grade 3/4 AEs, and all-causality dose reduction of any study intervention due to AEs and dose interruption of any study intervention due to AEs were higher (≥10% difference) in the EC + mFOLFOX6 Arm than the Control Arm.

Table 23. Applicant - Overview of Adverse Events - Phase 3 Safety Set (Protocol C4221015)

Adverse Event Category	EC (N=154) n (%)	EC+mFOLFOX6 (N=231) n (%)	Control (N=228) n (%)
Number (%) of Participants with AEs (All Causality)			
Any AEs	149 (96.8)	230 (99.6)	223 (97.8)
Any Serious AEs	39 (25.3)	87 (37.7)	79 (34.6)
AEs with Maximum CTCAE Grade 3 or 4	61 (39.6)	171 (74.0)	139 (61.0)
AEs with Maximum CTCAE Grade 5	2 (1.3)	10 (4.3)	10 (4.4)
Dose reduction of any study intervention due to AE	16 (10.4)	141 (61.0)	109 (47.8)
Dose reduction of encorafenib due to AE	13 (8.4)	51 (22.1)	0 (0.0)
Dose reduction of cetuximab due to AE	4 (2.6)	14 (6.1)	0 (0.0)
Dose reduction of other study intervention[a] due to AE	1 (0.6)	129 (55.8)	109 (47.8)
Dose interruption of any study intervention due to AE	59 (38.3)	196 (84.8)	146 (64.0)
Dose interruption of encorafenib due to AE	55 (35.7)	131 (56.7)	1 (0.4)
Dose interruption of cetuximab due to AE	46 (29.9)	135 (58.4)	3 (1.3)
Dose interruption of other study intervention[a] due to AE	2 (1.3)	175 (75.8)	146 (64.0)
AE leading to discontinuation of any study intervention	14 (9.1)	48 (20.8)	34 (14.9)
Permanent discontinuation of encorafenib due to AE	11 (7.1)	27 (11.7)	0 (0.0)
Permanent discontinuation of cetuximab due to AE	14 (9.1)	30 (13.0)	0 (0.0)
Permanent discontinuation of other study intervention[a] due to AE	0 (0.0)	36 (15.6)	34 (14.9)
Number (%) of Participants with Treatment-related AEs			
Related to Any Study Intervention	135 (87.7)	228 (98.7)	212 (93.0)
Treatment-related AEs with Maximum CTCAE Grade 3 or 4	24 (15.6)	161 (69.7)	123 (53.9)
Treatment-related AEs with Maximum CTCAE Grade 5	0 (0.0)	0 (0.0)	1 (0.4)
AEs related to encorafenib	121 (78.6)	196 (84.8)	1 (0.4)
AEs related to cetuximab	122 (79.2)	197 (85.3)	1 (0.4)
AEs related to other study intervention[a]	15 (9.7)	223 (96.5)	212 (93.0)
Serious AEs related to any study intervention	9 (5.8)	42 (18.2)	44 (19.3)
AEs Associated with COVID-19			
Number (%) of Participants with AEs Associated with Reduction of Any Study Intervention Due to COVID-19	0 (0.0)	0 (0.0)	1 (0.4)
Number (%) of Participants with AEs Associated with Discontinuation of Any Study Intervention Due to COVID-19	0 (0.0)	1 (0.4)	0 (0.0)

Table 23. Applicant - Overview of Adverse Events - Phase 3 Safety Set (Protocol C4221015)

Adverse Event Category	EC (N=154) n (%)	EC+mFOLFOX6 (N=231) n (%)	Control (N=228) n (%)

MedDRA v26.1 coding dictionary applied.
AE must be treatment-emergent to be included in this table.
a. Other study intervention includes: irinotecan, oxaliplatin, leucovorin or levo-leucovorin, fluorouracil (bolus or infusion), capecitabine, and bevacizumab (as appropriate for the treatment group).
Dose reduction of other study intervention is defined as reduction of at least one drug.
Dose interruption of other study intervention is defined as temporary stop of at least one drug or permanent stop of at least one (but not all) drugs.
Permanent discontinuation of other study intervention is defined as permanent stop of all drugs.
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:51) Source Data: adae Table Generation: 16APR2024 (19:34) (Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR PCD/C4221015_PH3_20240319_Unblinded/adae_s130_p3
Table 14.3.1.1.1.1 encorafenib is for Pfizer internal use.

Most Frequent AEs by Preferred Term

A summary of all-causality AEs by PT reported for ≥10% of participants in any Phase 3 treatment arm is provided in Table 24.

All-causality AEs occurred in 99.6% EC + mFOLFOX6 Arm and 97.8% Control Arm.

- The most frequent (≥20% of participants) all-causality AEs by PT in the EC + mFOLFOX6 Arm were nausea (51.1%), anemia (36.4%), diarrhea (34.2%), decreased appetite and vomiting (33.3% each), and neutrophil count decreased (32.0%), asthenia (26.8%), pyrexia (26.0%), peripheral sensory neuropathy and rash (24.7% each), fatigue (24.2%), neuropathy peripheral (23.4%), arthralgia and neutropenia (22.1% each), alopecia (21.2%), and constipation (20.3%); and in the Control Arm were nausea (48.2%), diarrhea (46.9%), neutrophil count decreased (28.1%), decreased appetite and fatigue (25.0% each), anemia (22.8%), neutropenia (22.4%), peripheral sensory neuropathy (21.5%), neuropathy peripheral and vomiting (21.1% each), and abdominal pain (20.6%).
  - All-causality AEs of anemia (36.4% vs 22.8%), vomiting (33.3% vs 21.1%), asthenia (26.8% vs 14.5%), pyrexia (26.0% vs 13.6%), rash (24.7% vs 2.6%), arthralgia (22.1% vs 3.5%), alopecia (21.2% vs 10.1%) lipase increased (19.9% vs 9.6%), skin hyperpigmentation (16.9% vs 2.2%), and dermatitis acneiform (15.2% vs 0.4%) were reported with higher frequency (≥10% difference) in the EC + mFOLFOX6 Arm than the Control Arm.
  - All-causality AEs of diarrhea (34.2% vs 46.9%) were reported with lower frequency (≥10% difference) in the EC + mFOLFOX6 Arm than the Control Arm.
- Among all-causality hematologic AEs, anemia (36.4% vs 22.8%) was the most commonly reported AE with a higher frequency (≥10% difference) in the EC + mFOLFOX6 Arm than the Control Arm. Thrombocytopenia (11.3% vs 7.9%) and platelet count decreased (19.9%

vs 12.3%) were also reported with higher frequencies (≤10% difference) in the EC + mFOLFOX6 Arm vs Control Arm. Neutropenia (22.1% vs 22.4%) and neutrophil count decreased (32.0% vs 28.1%) were reported with similar frequencies in the EC + mFOLFOX6 Arm and the Control Arm, with febrile neutropenia reported infrequently (2.6% vs 4.4%).

- Among all-causality non-hematologic AEs, nausea (51.1% vs 48.2%), as well as neuropathy-associated AEs (peripheral sensory neuropathy [24.7% vs 21.5%], neuropathy peripheral [23.4% vs 21.1%], paresthesia [12.1% vs 7.9%], and neurotoxicity [10.8% vs 7.9%]) were reported with similar frequencies in the EC + mFOLFOX6 Arm and the Control Arm. As expected, asthenia (26.8% vs 14.5%), pyrexia (26.0% vs 13.6%), arthralgia (22.1% vs 3.5%), rash (24.7% vs 2.6%), and other dermatologic events were reported with higher frequencies in the EC + mFOLFOX6 Arm than the Control Arm.

Treatment-related AEs occurred in 98.7% EC + mFOLFOX6 Arm and 93.0% Control Arm

- The most frequent (≥20% of participants) treatment-related AEs by PT in the EC + mFOLFOX6 Arm were nausea (48.5%), neutrophil count decreased (31.6%), vomiting (31.2%), decreased appetite (29.4%), anemia (26.8%), diarrhea and peripheral sensory neuropathy (24.7% each), rash (23.4%), fatigue and neuropathy peripheral (22.9% each), neutropenia (21.6%), and alopecia and asthenia (21.2% each); and in the Control Arm were nausea (45.2%), diarrhea (43.4%), neutrophil count decreased (28.1%), fatigue (22.4%), neutropenia (21.9%), peripheral sensory neuropathy (21.5%), and neuropathy peripheral (20.6%).

Table 24. Applicant - Decreasing Frequency of Treatment Emergent Adverse Events by PT in >= 10% in Any Phase 3 Treatment Arm (All Causalities) - Phase 3 Safety Set (Protocol C4221015)

Number of Participants Evaluable for AEs	EC (N=154)	EC+mFOLFOX6 (N=231)	Control (N=228)
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)
With Any Adverse Event	149 (96.8)	230 (99.6)	223 (97.8)
Nausea	30 (19.5)	118 (51.1)	110 (48.2)
Anaemia	28 (18.2)	84 (36.4)	52 (22.8)
Diarrhoea	25 (16.2)	79 (34.2)	107 (46.9)
Decreased appetite	23 (14.9)	77 (33.3)	57 (25.0)
Vomiting	20 (13.0)	77 (33.3)	48 (21.1)
Neutrophil count decreased	2 (1.3)	74 (32.0)	64 (28.1)
Asthenia	25 (16.2)	62 (26.8)	33 (14.5)
Pyrexia	25 (16.2)	60 (26.0)	31 (13.6)
Peripheral sensory neuropathy	3 (1.9)	57 (24.7)	49 (21.5)
Rash	26 (16.9)	57 (24.7)	6 (2.6)
Fatigue	33 (21.4)	56 (24.2)	57 (25.0)
Neuropathy peripheral	1 (0.6)	54 (23.4)	48 (21.1)

Table 24. Applicant - Decreasing Frequency of Treatment Emergent Adverse Events by PT in >= 10% in Any Phase 3 Treatment Arm (All Causalities) - Phase 3 Safety Set (Protocol C4221015)

Number of Participants Evaluable for AEs	EC (N=154)	EC+mFOLFOX6 (N=231)	Control (N=228)
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)
Arthralgia	52 (33.8)	51 (22.1)	8 (3.5)
Neutropenia	3 (1.9)	51 (22.1)	51 (22.4)
Alopecia	12 (7.8)	49 (21.2)	23 (10.1)
Constipation	21 (13.6)	47 (20.3)	44 (19.3)
Lipase increased	10 (6.5)	46 (19.9)	22 (9.6)
Platelet count decreased	4 (2.6)	46 (19.9)	28 (12.3)
White blood cell count decreased	2 (1.3)	42 (18.2)	32 (14.0)
Weight decreased	12 (7.8)	40 (17.3)	19 (8.3)
Skin hyperpigmentation	19 (12.3)	39 (16.9)	5 (2.2)
Abdominal pain	24 (15.6)	38 (16.5)	47 (20.6)
Dermatitis acneiform	29 (18.8)	35 (15.2)	1 (0.4)
Hypokalaemia	9 (5.8)	30 (13.0)	22 (9.6)
Aspartate aminotransferase increased	11 (7.1)	29 (12.6)	25 (11.0)
Dry skin	22 (14.3)	29 (12.6)	8 (3.5)
Headache	23 (14.9)	29 (12.6)	17 (7.5)
Mucosal inflammation	5 (3.2)	29 (12.6)	22 (9.6)
Paraesthesia	0	28 (12.1)	18 (7.9)
Dysgeusia	8 (5.2)	27 (11.7)	31 (13.6)
Epistaxis	8 (5.2)	27 (11.7)	28 (12.3)
Hypomagnesaemia	14 (9.1)	27 (11.7)	9 (3.9)
Stomatitis	7 (4.5)	27 (11.7)	32 (14.0)
Alanine aminotransferase increased	12 (7.8)	26 (11.3)	22 (9.6)
Myalgia	29 (18.8)	26 (11.3)	9 (3.9)
Thrombocytopenia	1 (0.6)	26 (11.3)	18 (7.9)
Neurotoxicity	0	25 (10.8)	18 (7.9)
Palmar-plantar erythrodysaesthesia syndrome	3 (1.9)	25 (10.8)	18 (7.9)
Pruritus	26 (16.9)	24 (10.4)	4 (1.8)
Hypoalbuminaemia	8 (5.2)	23 (10.0)	13 (5.7)
Insomnia	13 (8.4)	23 (10.0)	13 (5.7)
Back pain	21 (13.6)	17 (7.4)	14 (6.1)
Melanocytic naevus	20 (13.0)	10 (4.3)	0
Hypertension	3 (1.9)	9 (3.9)	30 (13.2)

Table 24. Applicant - Decreasing Frequency of Treatment Emergent Adverse Events by PT in >= 10% in Any Phase 3 Treatment Arm (All Causalities) - Phase 3 Safety Set (Protocol C4221015)

Number of Participants Evaluable for AEs	EC (N=154)	EC+mFOLFOX6 (N=231)	Control (N=228)
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)

(@@) Denotes AE terms that were not coded by the MedDRA dictionary.
MedDRA v26.1 coding dictionary applied.
Preferred terms are sorted in descending frequency of EC+mFOLFOX6 column.
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:51) Source Data: adae Table Generation: 16APR2024 (19:54) (Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR PCD/C4221015 PH3 20240319 Unblinded/adae s180 p3
Table 14.3.1.2.1.1 encorafenib is for Pfizer internal use.

AESIs

The BREAKWATER Phase 3 encorafenib AESIs are discussed in this section. A review of encorafenib AESIs for the EC + mFOLFOX6 Arm of Phase 3 and the EC + mFOLFOX6 Cohort of the SLI presented side-by-side and as a pooled population is provided in Section 8.2.11 of this document.

All-causality encorafenib AESIs occurred in 73.2% EC + mFOLFOX6 Arm and 61.8% Control Arm (Table 31).

- The most frequent (≥10% of participants) all-causality encorafenib AESI by grouping in the EC + mFOLFOX6 Arm and the Control Arm was MYELOSUPPRESSION (71.9% and 60.5%, respectively) (Table 32).
- Other AESIs (CUTANEOUS NON-SQUAMOUS CELL CARCINOMA, HEPATIC FAILURE, and QT PROLONGATION) were reported in <6% of participants in each arm and with <5% difference between the EC + mFOLFOX6 Arm and the Control Arm. FACIAL PARESIS was not reported in participants in either arm.
- Nearly half of all-causality encorafenib AESIs were Grade 1 or 2 in severity in both treatment arms.
- All-causality Grade 3 encorafenib AESIs were reported in 32.0% EC + mFOLFOX6 Arm and 25.0% Control Arm; the most frequent (≥5% of participants) by grouping in the EC + mFOLFOX6 Arm and the Control Arm was MYELOSUPPRESSION (30.7% and 24.6%, respectively).
- All-causality Grade 4 encorafenib AESIs were reported in 10.8% EC + mFOLFOX6 Arm and 7.5% Control Arm; the most frequent (≥5% of participants) by grouping in the EC + mFOLFOX6 Arm and the Control Arm was MYELOSUPPRESSION (10.8% and 7.5%, respectively).

- No all-causality Grade 5 encorafenib AESIs were reported in the EC + mFOLFOX6 Arm. One participant (0.4%) in the Control Arm had a Grade 5 encorafenib AESI of QT PROLONGATION (PT of cardiac arrest considered not treatment related).
- Most AESIs were considered treatment related; the percentage of participants with treatment-related encorafenib AESIs was 69.3% EC + mFOLFOX6 Arm and 59.2% Control Arm.

All-causality encorafenib serious AESIs occurred in 5.6% EC + mFOLFOX6 Arm and 5.3% Control Arm (Table 31).

- The most frequent all-causality encorafenib serious AESI by grouping in the EC + mFOLFOX6 Arm and the Control Arm was MYELOSUPPRESSION (4.3% and 4.4%, respectively) (Table 33).
- Most serious AESIs were considered treatment related; the percentage of participants with treatment-related encorafenib serious AESIs was 4.3% EC + mFOLFOX6 Arm and 4.8% Control Arm.

ADRs

ADRs (AEs for which a causal relationship between study treatment and the AE was at least a reasonable possibility) were defined as either a single MedDRA PT or a grouping of PTs. Grouped terms were used in some cases because the frequency of certain medical concepts or conditions could be underestimated by the reliance on single MedDRA PTs. Thus, certain PTs were analyzed in aggregate using these grouped terms. ADR terms that are grouped in aggregate are presented using capital letters in the sections that describe ADRs; ADRs that represent a single PT are presented using lowercase letters. For ADRs, AEs were coded using MedDRA Version 26.1.

For the BREAKWATER study, ADRs were initially based on the ADRs identified in the mCRC sNDA for EC in *BRAF* V600E-mutant mCRC in the BEACON study, as it represents the established safety profile for the combination of encorafenib and cetuximab being evaluated in BREAKWATER. As such, these established ADRs are considered to be a foundational starting point for the BREAKWATER ADRs. However, the determination of ADRs for BREAKWATER was not limited to just those ADRs identified in the BEACON study. For BREAKWATER, additional consideration (based on internal clinical and safety review of the totality of safety data with respect to frequency, severity, and listed ADRs of individual study drugs) was undertaken in identifying any new potential ADRs that are uniquely and likely associated with the combination (encorafenib + cetuximab + chemotherapy, regardless of association with encorafenib, cetuximab, or chemotherapy) specific to BREAKWATER. A review of ADRs for the EC + mFOLFOX6 Arm of Phase 3 and the EC + mFOLFOX6 Cohort of the SLI presented side-by-side and as a pooled population is provided in Section 8.2.11 of this document.

ADRs are summarized and provided in Table 34. The most frequent ADRs (≥25% of participants, all grades) by ADR term in the EC + mFOLFOX6 Arm were NEUROPATHY PERIPHERAL (61.9%), nausea (51.1%), fatigue (49.4%), ANEMIA (38.1%), diarrhea (34.2%), decreased appetite and vomiting (33.3% each), RASH (30.7%), HEMORRHAGE (29.9%), and ABDOMINAL PAIN and PYREXIA (26.4% each); and in the Control Arm were

NEUROPATHY PERIPHERAL (53.1%), nausea (48.2%), diarrhea (46.9%), fatigue (37.7%), ABDOMINAL PAIN (27.2%), ANEMIA (25.4%), and decreased appetite (25.0%).

Newly Identified ADRs/Risks
ADRs of alopecia, lipase increased, and ANEMIA were identified as new with respect to the initial sNDA for mCRC, but are known ADRs for encorafenib in combination with binimetinib in other indications and/or as a single agent.

The Applicant's Position:
AEs in the EC + mFOLFOX6 Arm were generally consistent with the known safety profiles of each agent, and no new safety signals were identified. The most frequent (≥30% of participants) all-causality AEs in the EC + mFOLFOX6 Arm were nausea (51.1%), anemia (36.4%), diarrhea (34.2%), decreased appetite and vomiting (33.3% each), and neutrophil count decreased (32.0%).

Encorafenib AESIs in the EC+mFOLFOX6 Arm were generally consistent with the known safety profile of encorafenib, with some expected overlap with the safety profiles of cetuximab and/or chemotherapy. The most frequent all-causality encorafenib AESI by grouping in the EC + mFOLFOX6 Arm and in the Control Arm was MYELOSUPPRESSION (71.9% and 60.5%, respectively), mainly driven by frequent reporting of anemia and neutrophil count decreased/neutropenia. Other AESIs were reported in <6% of participants in each arm and with <5% difference between the EC + mFOLFOX6 Arm and the Control Arm.

The ADRs for the EC + mFOLFOX6 combination in participants with *BRAF* V600E-mutant mCRC in BREAKWATER were consistent with those for the EC combination in BEACON in addition to the newly identified ADRs of alopecia, lipase increased, and ANEMIA. However, these additional ADRs are known ADRs for encorafenib in combination with binimetinib in other indications and/or as a single agent.

The analysis of all relevant data pertinent to the serious adverse reactions resulted in the affirmation of events listed in the current Warnings and Precautions sections of the current encorafenib USPI in the mCRC population (BRAFTOVI [encorafenib] USPI, 2023).

The FDA's Assessment:
For the safety analysis, FDA combined analogous or closely related preferred terms (PTs) into custom grouped terms (GTs) that are clinically relevant as outlined earlier in Section 8.2.3. Laboratory abnormalities reported under SOCs 'Investigations' and 'Metabolism And Nutrition Disorders' in the AE data were excluded from the TEAEs analysis and instead assessed separately in the Laboratory Findings section.

The comparison to the control arm with respect to the contribution of components regarding the safety of encorafenib and cetuximab was impacted by the administration of three different regimens in the control arm (with use of bevacizumab). As such, it is difficult to clearly delineate the additional toxicity of E+C (possibly excepting dermatological toxicity that is likely attributed to cetuximab).

FDA did not perform an independent analysis of the incidence of drug-related adverse reactions. Treatment-emergent adverse events (TEAEs) were reported in 99.6% of all patients in the

investigational arm, compared to 97.8% in the control arm.

The most common TEAEs excluding laboratory abnormalities reported in the EC + mFOLFOX6 in greater than 10% of patients by SOC and PT or GT presented in the Table 25.

TEAEs that were reported in greater than ≥30% of patients in the EC + mFOLFOX6 arm were neuropathy peripheral (62%), nausea (51%), fatigue (49%), diarrhea (34%), vomiting and decreased appetite (33% each), and rash (31%). In general, the addition of encorafenib with cetuximab to mFOLFOX6 chemotherapy was associated with an increase in reported events of cutaneous toxicity, hemorrhages and musculoskeletal pain as compared to the chemotherapy control arm. AEs reported with the higher difference (≥10%) for All Grade TEAEs in the EC + mFOLFOX6 Arm compared to control arm were: fatigue (49% vs 38%), vomiting (33% vs 21%), rash (31% vs 4%), hemorrhage (30% vs 18%), pyrexia (26% vs 13%), arthralgia (23% vs 4%) and alopecia (21% vs 10%) Table 26.

Table 25. Treatment Emergent Adverse Events by SOC and PT occurred in >= 10% in EC+mFOLFOX6 Treatment Arm in Phase 3

	EC + mFOLFOX6 (n=231)		Control Arm (n=228)	
Number (%) of patients by System Organ Class and Preferred Terms	**All grades n (%)**	**Grade 3 or 4 n (%)**	**All grades n (%)**	**Grade 3 or 4 n (%)**
Nervous System Disorders				
Neuropathy Peripheral (GT)	143 (62)	34 (15)	121 (53)	14 (6)
Headache	29 (13)	1 (0.4)	17 (7)	0
Dysgeusia	27 (12)	0 (0.0)	31 (14)	0
Neurotoxicity	25 (11)	11 (5)	18 (8)	0
Gastrointestinal Disorders				
Nausea	118 (51)	6 (3)	110 (48)	7 (3)
Diarrhoea (GT)	79 (34)	3 (1)	110 (48)	11 (5)
Vomiting (GT)	77 (33)	8 (4)	48 (21)	5 (2)
Abdominal Pain (GT)	61 (26)	8 (4)	62 (27)	3 (1)
Constipation	47 (20)	1 (0.4)	44 (19)	1 (0.4)
Skin And Subcutaneous Tissue Disorders				
Rash (GT)	71 (31)	2 (1)	8 (4)	0
Alopecia	49 (21)	0	22 (10)	0
Dry Skin	40 (17)	0	9 (4)	0
Skin Hyperpigmentation	39 (17)	0	5 (2)	0
Dermatitis acneiform	39 (17)	2 (1)	2 (1)	0
Pruritus	24 (10)	0	4 (2)	0
Vascular Disorders				
Hemorrhage (GT)	69 (30)	6 (3)	41 (18)	2 (1)

Musculoskeletal And Connective Tissue Disorders				
Arthralgia (GT)	53 (23)	2 (1)	8 (4)	0
Myopathy (GT)	33 (14)	0	16 (7)	1 (0.4)
General Disorders And Administration Site Conditions				
Fatigue (GT)	114 (49)	15 (6)	86 (38)	9 (4)
Pyrexia (GT)	61 (26)	4 (2)	30 (13)	1 (0.4)
Metabolism And Nutrition Disorders				
Decreased Appetite	77 (33)	5 (2)	57 (25)	3 (1)
Psychiatric disorders				
Insomnia	23 (10)	0	13 (6)	0

Table 26. Treatment Emergent Adverse Events Observed ≥20% and with Difference ≥10% in EC + mFOLFOX6 Treatment Arm Compared with Control Arm in Phase 3

	EC + mFOLFOX6 (n=231)		Control Arm (n=228)	
Percentage of Patients by Preferred Terms	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Fatigue (GT)	49	6	38	4
Vomiting (GT)	33	4	21	2
Rash (GT)	31	1	4	0
Hemorrhage (GT)	30	3	18	1
Pyrexia (GT)	26	2	13	<1
Arthralgia (GT)	23	1	4	0
Alopecia	21	0	10	0

FDA agrees with the applicant's strategy for defining and grouping of the adverse events of special interest (AESIs) for encorafenib that are clinically relevant and have overlapping potential with chemotherapy agents of mFOLFOX6. The identified AESIs of myelosuppression, QT prolongation, hepatic failure, cutaneous non-squamous cell carcinoma, facial paresis, were reviewed and analyzed within the context of the overall safety data observed in the BREAKWATER trial and prior experience with encorafenib in mCRC and other indications.

The incidence of AESIs reported for the EC + mFOLFOX6 Arm of Phase 3 and pooled populations were similar.

The frequencies of the AESI were reported in a higher rate in the EC + mFOLFOX6 Arm versus the control arm (73 % vs 62%) with the majority of them represented by the events of myelosuppression (72% and 61%). Serous AESIs of myelosuppression were reported at the same frequency in both arms (4.3% and 4.4%).

The analysis of relevant data, including significant serious adverse events and AESIs, did not identify any events beyond those currently included in the Warning and Precautions section of the encorafenib U.S. Prescribing Information (also considering the expected toxicity of the concomitant cytotoxic chemotherapy). FDA agrees that no changes to the Warning and Precautions section are warranted at this time (with respect to adding or removing a Warning).

Laboratory Findings

Data:

Individual changes in laboratory test parameters that were determined to be clinically relevant were reported as AEs and are described in the relevant sections above. Notable shifts from baseline for hematology/coagulation and chemistry are summarized below.

Hematology and Coagulation

Shifts from Grade ≤2 at baseline to Grade 3 or 4 at post-baseline in hematology and coagulation laboratory values are provided in Table 28.

- The most frequent hematology and coagulation parameters that shifted from Grade ≤2 at baseline to Grade 3 post baseline (≥10% of participants) in the EC + mFOLFOX6 Arm were neutrophil count decreased (24.3%), anemia (13.2%), and WBC decreased (11.0%); and in the Control Arm was neutrophil count decreased (25.0%).
- The most frequent hematology and coagulation parameter that shifted from Grade ≤2 at baseline to Grade 4 post baseline (≥5% of participants) in the EC + mFOLFOX6 Arm and the Control Arm was neutrophil count decreased (11.9% and 8.5%, respectively).

Chemistries

Shifts from Grade ≤2 at baseline to Grade 3 or 4 at post-baseline chemistry laboratory values are provided in Table 29.

- The most frequent chemistry parameters that shifted from Grade ≤2 at baseline to Grade 3 post baseline (≥10% of participants) in the EC + mFOLFOX6 Arm and the Control Arm was lipase increased (39.4% and 24.0%, respectively).
- The most frequent chemistry parameter that shifted from Grade ≤2 at baseline to Grade 4 post baseline (≥5% of participants) in the EC + mFOLFOX6 Arm was lipase increased (11.1%). There were no chemistry parameters that shifted from Grade ≤2 at baseline to Grade 4 post baseline reported in ≥5% of participants in the Control Arm; the most frequent (≥1% of participants) was lipase increased (1.5%).

Liver Function Tests

- One (0.4%) participant in the EC + mFOLFOX6 Arm and none in the Control Arm had liver function test values that met case finding criteria for Hy's law (defined as concurrent ALT or AST ≥3 × ULN & TBILI ≥2 × ULN & ALP ≤2 × ULN or missing).
    - One participant in the EC + mFOLFOX6 Arm met the case finding criteria for a potential Hy's Law case due to ALT or AST ≥3 × ULN & TBILI ≥2 × ULN with a missing ALP value, thus limiting full clinical assessment of this participant's hepatic profile. Also of relevance is the participant's ongoing medical history of hepatic cysts, with no clinical hepatic events reported.

The Applicant's Position:

There were no potentially clinically important abnormalities in laboratory test results between the EC + mFOLFOX6 Arm and the Control Arm. The most frequently reported hematology parameters that shifted from Grade ≤2 at baseline to Grade 3 and 4 post baseline were mainly driven by the expected myelosuppressive impact of the mFOLFOX6 regimen. One participant in the EC + mFOLFOX6 Arm met the case finding criteria for a potential Hy's Law case due to ALT or AST ≥3 × ULN & TBILI ≥2 × ULN with a missing ALP value, thus full clinical assessment of this participant's hepatic profile was limited, and no clinical hepatic events were reported. There were no notable LFT findings that would necessitate a change in the current information in the label.

The FDA's Assessment:
FDA conducted an analysis of laboratory abnormalities calculating the incidence rate of the worst-grade laboratory findings using the number of patients with both baseline and post-treatment values as the denominator (varied from 215 to 227 in investigational arm and from 203 to 214 in the control arm). Laboratory abnormality analysis for the EC + mFOLFOX6 Arm and Control Arm in Phase 3 BREAKWATER trial is summarized in the following Table 27.

The most frequently reported hematologic abnormalities in both arms were driven by myelosuppression that is expected overlapping toxicity for combination of encorafenib with cetuximab and chemotherapy agents. Significant myelosuppression observed in laboratory findings represented by neutrophils count decrease, white blood cells decreased, thrombocytopenia, hemoglobin decrease, and coagulation abnormalities.

Laboratory Grades 1- 4 hematological abnormalities that occurred with the higher incidence and greater than 10% difference in the EC + mFOLFOX6 Arm compared to the Control Arm were hemoglobin decreased (60% vs 47%), aPTT prolonged (59% vs 38%), and INR increase (39% vs 20%).

Grade 3-4 hemoglobin decrease was reported in 13% of patients in EC + mFOLFOX6 Arm and 5% in the Control Arm.

Notably, among chemistry abnormalities, lipase increase was observed at the significantly higher levels in EC + mFOLFOX6 Arm for All Grades (82% vs 54% in the Control Arm) and for Grade 3-4 (50% and 25% respectively). Although increased lipase was common, pancreatitis was rare (see below).

Hypokalemia and hypomagnesemia were also reported more frequently (>10%) in the EC + mFOLFOX6 arm. Hypomagnesemia and accompanying electrolyte abnormalities are known side effects of EGFR inhibitors.

Table 27. Laboratory Abnormalities Reported Most Frequently (≥20%) in Phase 3 of the BREAKWATER

Laboratory abnormality	EC + mFOLFOX6	Control Arm

	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Hematologic				
Neutrophil count decrease	63	36	60	34
White blood cell decreased	62	12	54	7
Hemoglobin decreased	60	13	47	5
Platelet count decreased	59	1	50	2
Activated partial thromboplastin time prolonged	59	3	38	2
INR increased	39	1	20	0.5
Chemistry				
Lipase Increased	82	50	54	25
Creatinine increased	55	1	57	0.5
Glucose increased	49	11	35	2
Alanine aminotransferase increased	39	1	40	2
Aspartate aminotransferase increased	36	1	35	2
Albumin decreased	36	0	24	1
Potassium decreased	33	4	19	4
Alkaline phosphatase increased	31	2	31	1
Magnesium decreased	23	1	11	0.5
Calcium decreased	23	4	16	2.3

Table 28. Applicant - Shift from Grade <= 2 at Baseline to Grade >= 3 Post-baseline (Hematology and Coagulation) - Phase 3 Safety Set (Protocol C4221015)

Parameter	EC			EC+mFOLFOX6			Control		
	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)
Activated partial thromboplastin time prolonged	149	7 (4.7)	0	228	8 (3.5)	0	214	4 (1.9)	0
Anemia	149	10 (6.7)	0	227	30 (13.2)	0	215	12 (5.6)	0
Hemoglobin increased	149	1 (0.7)	0	228	1 (0.4)	0	215	0	0
INR increased	148	0	0	227	1 (0.4)	0	214	1 (0.5)	0
Leukocytosis	149	1 (0.7)	0	228	1 (0.4)	0	214	1 (0.5)	0
Neutrophil count decreased	149	5 (3.4)	1 (0.7)	226	55 (24.3)	27 (11.9)	212	53 (25.0)	18 (8.5)
Platelet count decreased	149	0	0	228	3 (1.3)	0	215	2 (0.9)	3 (1.4)
White blood cell decreased	149	0	1 (0.7)	228	25 (11.0)	4 (1.8)	214	14 (6.5)	2 (0.9)

N = the number of participants in the safety analysis set with baseline (<= grade 2 or missing) and at least one post-baseline assessment for each parameter in each treatment group.
n = the number of participants with post-baseline meeting criteria (>= grade 3).
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:52) Source Data: adlb Table Generation: 15APR2024 (19:26)
(Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR PCD/C4221015_PH3_20240319_Unblinded/adlb_s518_p3
Table 14.3.4.1.3.1 encorafenib is for Pfizer internal use.

Table 29. Applicant - Shift from Grade <= 2 at Baseline to Grade >= 3 Post-baseline (Chemistries) - Phase 3 Safety Set (Protocol C4221015)

Parameter	EC			EC+mFOLFOX6			Control		
	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)
Alanine aminotransferase increased	150	2 (1.3)	0	227	3 (1.3)	0	215	4 (1.9)	0
Alkaline phosphatase increased	145	4 (2.8)	0	218	4 (1.8)	1 (0.5)	208	3 (1.4)	0
Aspartate aminotransferase increased	149	0	0	228	2 (0.9)	0	214	3 (1.4)	1 (0.5)
Blood bilirubin increased	150	4 (2.7)	0	228	2 (0.9)	1 (0.4)	215	1 (0.5)	0
Creatinine increased	150	3 (2.0)	1 (0.7)	228	3 (1.3)	0	215	1 (0.5)	0
Hypercalcemia	150	0	0	228	0	0	214	1 (0.5)	0
Hyperglycemia	149	6 (4.0)	0	225	21 (9.3)	4 (1.8)	212	4 (1.9)	1 (0.5)
Hyperkalemia	150	1 (0.7)	0	228	0	0	214	0	0
Hypermagnesemia	150	2 (1.3)	0	228	4 (1.8)	1 (0.4)	214	2 (0.9)	0
Hypernatremia	150	0	0	228	0	1 (0.4)	215	1 (0.5)	1 (0.5)
Hypoalbuminemia	150	0	0	228	0	0	215	2 (0.9)	0
Hypocalcemia	150	3 (2.0)	1 (0.7)	227	6 (2.6)	3 (1.3)	214	4 (1.9)	1 (0.5)
Hypoglycemia	150	0	0	228	0	0	214	0	0
Hypokalemia	150	1 (0.7)	1 (0.7)	228	7 (3.1)	1 (0.4)	214	10 (4.7)	0
Hypomagnesemia	150	2 (1.3)	0	228	1 (0.4)	1 (0.4)	214	1 (0.5)	0
Hyponatremia	147	5 (3.4)	0	226	4 (1.8)	0	213	8 (3.8)	0
Lipase increased	145	18 (12.4)	2 (1.4)	216	85 (39.4)	24 (11.1)	200	48 (24.0)	3 (1.5)

Table 29. Applicant - Shift from Grade <= 2 at Baseline to Grade >= 3 Post-baseline (Chemistries) - Phase 3 Safety Set (Protocol C4221015)

	EC			EC+mFOLFOX6			Control		
Parameter	**N**	**Grade 3 n (%)**	**Grade 4 n (%)**	**N**	**Grade 3 n (%)**	**Grade 4 n (%)**	**N**	**Grade 3 n (%)**	**Grade 4 n (%)**

N = the number of participants in the safety analysis set with baseline (<= grade 2 or missing) and at least one post-baseline assessment for each parameter in each treatment group.
n = the number of participants with post-baseline meeting criteria (>= grade 3).
PFIZER CONFIDENTIAL SDTM Creation: 02APR2024 (19:52) Source Data: adlb Table Generation: 15APR2024 (19:26)
(Data cutoff date : 22Dec2023 Database snapshot date : 19Mar2024) Output File: ./C4221015 P3 ORR PCD/C4221015 PH3 20240319 Unblinded/adlb s520 p3
Table 14.3.4.1.6.1 encorafenib is for Pfizer internal use.

Vital Signs

Data:

Blood Pressure

- Post-baseline high SBP values (≥160 mmHg and increase from baseline ≥20 mmHg) occurred in 3.1% EC + mFOLFOX6 Arm and 12.6% Control Arm, and post-baseline low SBP values (≤90 mmHg and decrease from baseline ≥20 mmHg) occurred in 7.0% EC + mFOLFOX6 Arm and none in the Control Arm.
- Post-baseline high DBP values (≥100 mmHg and increase from baseline ≥15 mmHg) occurred in 3.1% EC + mFOLFOX6 Arm and 10.3% Control Arm, and post-baseline low DBP values (≤50 mmHg and decrease from baseline ≥15 mmHg) occurred in 7.9% EC + mFOLFOX6 Arm and 0.5% Control Arm.

Pulse Rate

- Post-baseline abnormal high pulse rate values (≥120 bpm and increase from baseline ≥15 bpm) occurred in 3.9% EC + mFOLFOX6 Arm and 2.8% Control Arm, and post-baseline abnormal low pulse rate values (≤50 bpm and decrease from baseline ≥15 bpm) occurred in 0.4% EC + mFOLFOX6 Arm and 0.9% Control Arm.

Temperature

- Post-baseline high temperature values (≥37.5 °C) occurred in 7.9% EC + mFOLFOX6 Arm and 5.6% Control Arm, and post-baseline low temperature values (≤36 °C) occurred in 50.7% EC + mFOLFOX6 Arm and 47.7% Control Arm.

The Applicant's Position:

No clinically meaningful findings in the vital signs measurements or other observations related to safety were observed in this study.

The FDA's Assessment:

FDA agrees with the Applicant's analysis of vital sign assessments.

Electrocardiograms (ECGs)

Data:

- New QTcF > 500 ms occurred in 3.6% EC + mFOLFOX6 Arm and 1.0% Control Arm.
- An increase from baseline in QTcF of >60 msec occurred in 10.4% EC + mFOLFOX6 Arm and 2.9% Control Arm.

The Applicant's Position:

The assessments and observations in ECGs were as expected.

The FDA's Assessment:

The incidence of occurrence of QTcF > 500 ms in EC + mFOLFOX6 Arm is 3.6%, that is slightly higher than previously reported rates of encorafenib in combination with binimetinib and expected with the addition of chemotherapy agents. The QTc Prolongation is already listed as an adverse reaction with appropriate risk management strategies in the Section 5.Warning and Precautions of the encorafenib USPI.

QT

Data:
Refer to the ECG section for a description of QTc results.

The Applicant's Position:
Not applicable to this submission.

The FDA's Assessment:
Refer to the ECG section and 6.3.1. General Pharmacology QT/QTc prolongation section.

Immunogenicity

Data:
Not applicable to this submission.

The Applicant's Position:
No information is presented for encorafenib.

Immunogenicity and hypersensitivity information associated with cetuximab administration is presented in the current USPI for cetuximab (ERBITUX [cetuximab], 2021).

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.5. **Analysis of Submission-Specific Safety Issues**

Data:
There are no submission-specific safety issues to present.

The Applicant's Position:
Not applicable to this submission.

The FDA's Assessment:
FDA has no additional comments.

8.2.6. **Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

Data:
Not applicable to this submission.

The Applicant's Position:
Not applicable to this submission.

The FDA's Assessment:
FDA has no additional comments.

8.2.7. **Safety Analyses by Demographic Subgroups**
Data:

Age
In the Phase 3 EC + mFOLFOX6 Arm:

- The incidence of all-causality AEs (all grades) in participants <65 years (N=148) and ≥65 years (N=83) was 99.3% and 100.0%, respectively.
  - AEs (all grades) reported with higher frequency (difference of ≥10%) in participants <65 than in those ≥65 years were vomiting (37.8% vs 25.3%), peripheral sensory neuropathy (28.4% vs 18.1%), alopecia (25.7% vs 13.3%), abdominal pain (20.3% vs 9.6%), dermatitis acneiform (20.3% vs 6.0%), ALT increased (15.5% vs 3.6%), and epistaxis (17.6% vs 1.2%).
  - AEs (all grades) reported with lower frequency (difference of ≥10%) in participants <65 than in those ≥65 years were anemia (31.8% vs 44.6%), decreased appetite (29.7% vs 39.8%), neutropenia (17.6% vs 30.1%), and weight decreased (12.8% vs 25.3%).
- The participants in the EC + mFOLFOX6 Arm were primarily <75 years (N = 215). As such, there were too few participants in the ≥75 years (N=16) to make interpretable data comparisons between these age groups.

In the Phase 3 EC + mFOLFOX6 Arm:

- The incidence of all-causality AEs (all grades) in male participants (N=120) and female participants (N=111) was 99.2% and 100%, respectively.
  - No AEs (all grades) were reported with higher frequency (difference of ≥10%) in males than in females.
  - AEs (all grades) reported with lower frequency (difference of ≥10%) in males than in females were nausea (41.7% vs 61.3%), anemia (26.7% vs 46.8%), neutrophil count decreased (25.0% vs 39.6%), vomiting (22.5% vs 45.0%), alopecia (15.0% vs 27.9%), neutropenia (13.3% vs 31.5%), white blood cell count decreased (13.3% vs 23.4%), and mucosal inflammation (7.5% vs 18.0%).

Race
In the Phase 3 EC + mFOLFOX6 Arm:

- The incidence of all-causality AEs (all grades) in non-Asian participants (N=138) and Asian participants (N=86) was 99.3% and 100%, respectively.
  - AEs (all grades) reported with higher frequency (difference of ≥10%) in non-Asian participants than in Asian participants were fatigue (34.1% vs 9.3%), neutropenia (32.6% vs 4.7%), asthenia (29.0% vs 18.6%), neuropathy peripheral (29.0% vs 11.6%), mucosal inflammation (17.4% vs 3.5%), parasthesia (17.4% vs 4.7%), thrombocytopenia (15.9% vs 4.7%), and neurotoxicity (15.2% vs 3.5%).
  - AEs (all grades) reported with lower frequency (difference of ≥10%) in non-Asian participants than in Asian participants were decreased appetite (26.8% vs 45.3%), peripheral sensory neuropathy (21.0% vs 31.4%), neutrophil count decreased (19.6% vs

54.7%), platelet count decreased (10.1% vs 37.2%), skin hyperpigmentation (10.1% vs 26.7%), ALT increased (5.8% vs 20.9%), AST increased (5.8% vs 23.3%), white blood cell count decreased (5.1% vs 40.7%), hypoalbuminemia (4.3% vs 19.8%), malaise (1.4% vs 19.8%), and pigmentation disorder (0.7% vs 17.4%).

The Applicant's Position:

In the Phase 3 EC + mFOLFOX6 Arm, the overall incidence of all-causality AEs (all grades) was generally similar between age groups (<65 vs ≥65), [redacted] (male vs female), and race groups (non-Asian vs Asian), with the incidence of individual PTs varying between each of these subgroups. Sample size limitations preclude definitive conclusions regarding safety in the <75 vs ≥75-year subgroup.

The FDA's Assessment:

FDA`s exploratory analysis of safety conducted across age groups, [redacted] and racial subgroups (Asian vs. non-Asian) showed relatively similar incidence rates of all-grade and Grade 3-4 TEAEs. Differences in incidence rates of certain reported adverse events across subgroups by PTs/GTs are shown in Table 30.

Table 30. Analysis of TEAEs by Demographic Subgroups for Patients in EC + mFOLFOX6 Arm Phase 3

Age subgroups: < 65 years (n = 148) vs. ≥ 65 years (n = 83) *the separate analysis in subgroup of patients ≥75 years was not preformed based of the small sample size (n=16)*
○ All-grade TEAE incidence: 100% in patients <65 years vs 99.3% in subgroup ≥ 65 years ○ TEAEs observed with incidence higher than 10% in patients < 65 years vs. ≥ 65 years: • neuropathy peripheral GT (68% vs 53%), • vomiting (38% vs 25%), • hemorrhage GT (34% vs 22%), • alopecia (38% vs 13%) • dermatitis acneiform GT (22% vs 7%) ○ TEAEs observed with incidence higher than 10% in patients ≥ 65 years vs. < 65 years: • anemia (45% vs 32%), • decreased appetite (40% vs 30%), • neutropenia (30% vs 18%), • weight decreased (24% vs 13%).
[redacted] **subgroups: male (n = 120) vs. female (n = 111)**
○ All-grade TEAE incidence: 100% in males vs. 99.2% in females ○ TEAEs observed with incidence higher than 10% in females than in males: • nausea (61% vs 42%) • vomiting (45% vs 23 %) • abdominal pain (32% vs 22%) • rash GT (38% vs. 24%) • alopecia (28% vs 15%) • anemia (47% vs 27%)

• neutropenia (32% vs 13%) o No TEAEs were observed in males with an incidence at least 8% higher than in females
Race subgroups: White (n = 138) vs. Asian (n = 86) *the race subgroup was not reported for 7 patients*
o All-grade TEAE incidence: 100% in White vs. 93.3% in Asians o TEAEs observed with incidence higher than 10% in White patients than in Asian patients: • fatigue GT (61% vs 28%) • diarrhea (38% vs 28%) • rash GT (35% vs 26%) o TEAEs observed with incidence higher than 10% in Asian patients than in White patients: • decreased appetite (46% vs 27%) • malaise (20% vs 1.4%) • skin hyperpigmentation (27% vs 10%)

Additionally, a higher incidence of neutropenia and thrombocytopenia were reported in White patients versus Asians (33% vs 5% and 16% vs 5%, respectively) under the *SOC Blood and lymphatic system disorders*, while PTs neutrophil count decreased and platelets count decreased were reported more frequently in Asians under the *SOC Investigations* (55% vs 20 % and 37% vs 10%). These differences in laboratory findings across racial subgroups, based on data from the AE dataset, are not readily interpretable and are more likely attributable to variations in reporting practices and terminology across multiregional clinical sites.

FDA analysis of the adverse events by demographic subgroups did not identify any findings that are considered to be clinically significant or warrant an update to the encorafenib US prescribing information.

8.2.8. **Specific Safety Studies/Clinical Trials**

Data:
No new information in this submission.

The Applicant's Position:
Safety summaries were included as part of the BREAKWATER study; no specific safety studies were performed.

The FDA's Assessment:
FDA agrees with the applicant`s statement above.

8.2.9. **Additional Safety Explorations**

Human Carcinogenicity or Tumor Development

Data:
Carcinogenicity studies with encorafenib have not been conducted.

As described in the initial NDA for *BRAF* V600E/K-mutant melanoma, encorafenib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, or micronuclei in bone marrow of rats.

Based on its mechanism of action, encorafenib may promote malignancies associated with activation of *RAS* through mutation or other mechanisms.

The AESI of CUTANEOUS NON-SQUAMOUS CELL CARCINOMA was reported at an overall frequency of 1.3% EC + mFOLFOX6 Arm and 0.4% Control Arm (Table 32) (with the individual PT of basal cell carcinoma reported in 1.3% and 0.4%, respectively).

The ADR of SQUAMOUS CELL CARCINOMA was reported in 0.4% EC + mFOLFOX6 Arm and 0% Control Arm and the ADR of MALIGNANT MELANOMA was reported in 0.4% EC + mFOLFOX6 Arm and 0% Control Arm (Table 34).

The Applicant's Position:
New primary malignancies, including cutaneous and non-cutaneous, are a known class effect of BRAF inhibitors and are presented as Warnings and Precautions in the current USPI for encorafenib (BRAFTOVI [encorafenib] USPI, 2023).

The FDA's Assessment:
FDA agrees with the applicant's position. Warning and Precautions sections of the current U.S. Prescribing information for encorafenib includes communication of risk and management of new primary cutaneous malignancies.

Human Reproduction and Pregnancy

Data:
In nonclinical studies, embryo-lethal and skeletal developmental abnormalities were observed at high dose (exposures) of encorafenib in both rats and rabbits. In rabbits, small quantities of encorafenib were detected in fetal plasma, confirming placental transfer of encorafenib. It is not known whether encorafenib or its primary metabolite are present in human or animal milk. Thus, pregnant or lactating women were excluded from BREAKWATER. Also, women of childbearing potential were advised to use effective methods of contraception as described in the BREAKWATER study protocol. Males were also advised to take appropriate precautions to avoid fathering a child as described in the study protocol.

No participants with AEs of pregnancy or lactation were reported in BREAKWATER, as defined by the following MedDRA terms: Pregnancy, puerperium and perinatal conditions (SOC); Exposures associated with pregnancy, delivery and lactation (HLT); Lactation disorders (HLT); exposure via body fluid (PT); exposure via partner (PT); intoxication by breast feeding (PT); maternal drugs affecting fetus (PT); and paternal drugs affecting fetus (PT).

The Applicant's Position:
Based on the nonclinical findings with encorafenib, there is potential risk to a fetus and women of reproductive potential are advised to use an effective, non-hormonal method of contraception since encorafenib can render hormonal contraceptives ineffective, during treatment and for 2 weeks after the final dose of encorafenib as described in the current USPI for encorafenib (BRAFTOVI [encorafenib] USPI, 2023).

The FDA's Assessment:
FDA agrees with the Applicant's position. Current section 5.8 Embryo-Fetal Toxicity of the

encorafenib USPI effectively communicates the risk and contraception requirements for women of reproductive potential. Additional information regarding human reproductive risk and pregnancy risk can be found in the relevant sections of the encorafenib product label.

Pediatrics and Assessment of Effects on Growth

Data:
Not applicable to this submission.

The Applicant's Position:
The safety and effectiveness of encorafenib has not been established in pediatric patients.

The FDA's Assessment:
The Applicant was granted a full waiver of the requirement to conduct pediatric studies under PREA. Refer to **Section 10. Pediatrics** of this review for more information.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Overdose
Information regarding the administration of single-agent encorafenib above its indicated dose in the dose-escalation studies was previously reported in the initial NDA (NDA 210496).

No participants with AEs resulting from medication errors or overdose were identified in BREAKWATER, as defined by the following MedDRA terms: Overdoses NEC (HLT); Intentional product use issues (HLT); Intentional product misuses (HLT); and accidental overdose (PT).

Drug Abuse
No participants with AEs of abuse were identified in BREAKWATER, as defined by the following MedDRA PTs: drug abuser; drug use disorder; drug use disorder, antepartum; drug use disorder, postpartum; drug abuse; and substance abuse.

Withdrawal and Rebound
No participants with AEs related to withdrawal symptoms were identified in BREAKWATER, as defined by the following MedDRA HLT: Withdrawal and rebound effects.

The Applicant's Position:
There is no known antidote for encorafenib. Encorafenib (moderately protein bound) is unlikely to be dialyzable.

No new information about abuse potential of encorafenib was generated in support of this sNDA than was previously reported in the initial NDA (NDA 210496). Given the nature of encorafenib as an anticancer agent, it is considered to have an extremely low potential of abuse. No abuse studies have been performed.

No new information about withdrawal and rebound of encorafenib was generated in support of this sNDA. No studies have been conducted to assess withdrawal and rebound effects.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.10. **Safety in the Postmarket Setting**

Safety Concerns Identified Through Postmarket Experience

Data:

The EC + mFOLFOX6 combination has not yet been approved for the treatment of patients with *BRAF* V600E-mutant mCRC. Post-marketing experience has been obtained with the EC combination in *BRAF* V600E-mutant mCRC and is described in periodic aggregate reports that the Applicant has submitted to regulatory authorities, including the NDA Annual Report and PADERs submitted to the US FDA. The Applicant submitted 6 quarterly PADERs to the FDA since the first regulatory approval for CRC in the US on 08 April 2020 until 26 June 2021, and then 2 annual PADERs in 2022 and 2023.

The Applicant's Position:

The overall safety data from the EC combination originating from postmarketing sources in the CRC setting were consistent with the known safety profile of encorafenib and cetuximab. No new safety information or unusual trends were identified in the last submitted PADER for encorafenib.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety in the postmarket setting is expected to be similar to that observed in the clinical trial reviewed in this application.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.11. **Integrated Assessment of Safety**

Data:

This integrated assessment of safety presents pooled data for AESIs and ADRs from the EC + mFOLFOX6 Arm of Phase 3 and the EC + mFOLFOX6 Cohort of the SLI of the BREAKWATER study. Both AESI and ADR data from the EC + mFOLFOX6 Arm of Phase 3 and the EC + mFOLFOX6 Cohort of the SLI are presented side-by-side (separately for each cohort/arm) and as a POOLED population.

These summaries include data for 231 participants in the EC + mFOLFOX6 Arm of Phase 3 who received study treatment for a median duration of 28.1 weeks (range: 1.3 to 107.4 weeks), 27 participants in the EC + mFOLFOX6 Cohort of the SLI who received study treatment for a median duration of 37.9 weeks (range: 4.0 to 145.4 weeks), and 258 participants in the POOLED population.

AESIs

An overview of the encorafenib AESIs for Phase 3, the EC + mFOLFOX6 Cohort of the SLI, and the POOLED population is presented in Table 31.

- The overall frequencies of participants with all-causality encorafenib AESIs of any grade, and Grade 3 or 4 were generally consistent between the EC + mFOLFOX6 Arm of Phase 3 and the POOLED population.
- No Grade 5 AESIs were reported for participants who received EC + mFOLFOX6.

A summary of all-causality encorafenib AESIs by grouping for Phase 3, the EC + mFOLFOX6 Cohort of the SLI, and the POOLED population is provided in Table 32.

- The frequency of individual encorafenib AESIs was consistent (<1% difference) between the EC + mFOLFOX6 Arm of Phase 3 and the POOLED population. FACIAL PARESIS was not reported in participants who received EC + mFOLFOX6.

A summary of all-causality serious encorafenib AESIs by grouping for Phase 3, the EC + mFOLFOX6 Cohort of the SLI, and the POOLED population is provided in Table 33.

- The frequency of individual serious encorafenib AESIs was consistent (<1% difference) between the EC + mFOLFOX6 Arm of Phase 3 and the POOLED population.

ADRs
A summary of ADRs by SOC and ADR terms for Phase 3, the EC + mFOLFOX6 Cohort of the SLI, and the POOLED population is provided in Table 34.

- The most frequent ADRs (≥25% of participants, all grades) by ADR term in the POOLED population were NEUROPATHY PERIPHERAL (61.6%), nausea (53.5%), fatigue (50.4%), ANEMIA (36.8%), diarrhea (34.5%), vomiting (34.1%), decreased appetite (32.9%), RASH (32.2%), HEMORRHAGE (29.8%), PYREXIA (29.1%), and ABDOMINAL PAIN (27.9%).
- The frequency of individual ADR terms was consistent (<3% difference) between the EC + mFOLFOX6 Arm of Phase 3 and the POOLED population.

The Applicant's Position:
ADRs of alopecia, lipase increased, and ANEMIA were identified as new with respect to the initial sNDA for mCRC, but are known ADRs for encorafenib in combination with binimetinib in other indications and/or as a single agent. The overall (and individual) frequencies of encorafenib AESIs were generally consistent between the EC + mFOLFOX6 Arm of Phase 3 and the POOLED population. No new safety signals were identified based on assessments of AESIs.

The FDA's Assessment:
The safety assessment of the EC + mFOLFOX6 treatment combination is based primarily on the safety population of 231 patients with BRAFV600E-mutant mCRC received investigational regimen in Phase 3 Study of BREAKWATER study. The overall size of the safety population and the duration of exposure to the investigational treatment are sufficient to characterize the safety of the combination. The safety datasets are expected to be generalizable, considering their adequacy and overall representative demographic and clinical characteristics.

The safety profile of encorafenib in combination with cetuximab and mFOLFOX6 is generally acceptable in the context of treating the patients with metastatic advanced disease. The safety profile of the combination appears to be consistent with previously reported experiences for the regimen components when administered individually and the known effects of BRAF inhibitors,

EGFR inhibitors, and chemotherapy agents.

- Treatment emergent adverse events of any grade occurred in 100% and 98% of patients in the EC + mFOLFOX6 arm and the Control arm, respectively.
- Grade 3-4 events occurred in 74% and 61% of patients in the EC + mFOLFOX6 arm and the Control arm, respectively.
- Dose modifications of encorafenib required in 22% of patient and permanent treatment discontinuation of encorafenib in EC + mFOLFOX6 arm occurred in 12 % of patients.
- The most frequently reported AEs of all grades in patients treated with EC + mFOLFOX6 were peripheral neuropathy, fatigue, gastrointestinal, cutaneous toxicities, musculoskeletal disorders and hemorrhage.
- The most frequently reported hematologic laboratory abnormalities were mostly driven by myelosuppression, including decreased neutrophil counts, decreased white blood cell counts, thrombocytopenia, hemoglobin decreases, and coagulation abnormalities.
- Chemistry laboratory findings reported at the high rates were hypokalemia and hypomagnesemia, that are known side effects of EGFR inhibitors and are addressed in the cetuximab labeling information.
- Lipase increase was identified in 82% of patients and was the leading cause of dose modifications and discontinuation of the encorafenib, occurring in 1.7% in patients who discontinued the treatment and 2.6% of patients required dose reduction.
- An analysis of relevant data for significant SAEs and AESIs, did not identify any events beyond those currently included in the Warnings and Precautions section of the encorafenib U.S. Prescribing Information.

FDA did not identify any important new signals based on review of the safety data provided in this application. Of note, however, the control arm consisted of three different regimens such that they exact contribution of adverse events for EC in addition to chemotherapy is not clear.

FDA agrees that no changes to the Warning and Precautions section are warranted at this time (with respect to new Warnings). Dose modification guidelines for these toxicities are provided in the encorafenib U.S. Prescribing Information and effectively communicate risk mitigation and management strategies.

Table 31. Applicant - CRC - Summary of Clinical Safety Overview of Encorafenib Treatment-Emergent AESIs for Phase 3, Safety Lead-in and POOLED Set (Protocol C4221015)

Adverse Event Category	Phase 3 EC (N=154) n (%)	Phase 3 EC+mFOLFOX6 (N=231) n (%)	Phase 3 Control (N=228) n (%)	SLI EC+mFOLFOX6 (N=27) n (%)	Pooled EC+mFOLFOX6 (N=258) n (%)
Number (%) of Participants with AESIs (All Causality)					
Any AESIs	39 (25.3)	169 (73.2)	141 (61.8)	20 (74.1)	189 (73.3)
AESIs with Maximum CTCAE Grade 3 or 4	15 (9.7)	99 (42.9)	74 (32.5)	11 (40.7)	110 (42.6)
AESIs with Maximum CTCAE Grade 5	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Any Serious AESIs	0 (0.0)	13 (5.6)	12 (5.3)	2 (7.4)	15 (5.8)

MedDRA v26.1 coding dictionary applied.
Cut-off Date: BREAKWATER 22DEC2023
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 30APR2024 (17:52)
Output File: ./C4221015 P3 ORR PCD/ISS SCS ISE SCE 20240319 Unblinded/adae s130 folfox aesi p3
Table 14.3.1.2.3.101 encorafenib is for Pfizer internal use.

Table 32. Applicant - CRC - Summary of Clinical Safety Summary of Treatment-Emergent AESIs for Encorafenib, by Grouping Terms in Decreasing Frequency of All Grades (All Grades, Grade 3 or Higher) for Phase 3, Safety Lead-in and POOLED Set (All Causalities) (Protocol C4221015)

Number of Participants Evaluable for AEs	Phase 3 EC (N=154)		Phase 3 EC+mFOLFOX6 (N=231)		Phase 3 Control (N=228)		SLI EC+mFOLFOX6 (N=27)		Pooled EC+mFOLFOX6 (N=258)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
Number (%) of Participants: by GROUPING	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	39 (25.3)	15 (9.7)	169 (73.2)	99 (42.9)	141 (61.8)	75 (32.9)	20 (74.1)	11 (40.7)	189 (73.3)	110 (42.6)
MYELOSUPRESSION	33 (21.4)	13 (8.4)	166 (71.9)	96 (41.6)	138 (60.5)	73 (32.0)	20 (74.1)	11 (40.7)	186 (72.1)	107 (41.5)
QT PROLONGATION	8 (5.2)	3 (1.9)	13 (5.6)	6 (2.6)	3 (1.3)	3 (1.3)	2 (7.4)	2 (7.4)	15 (5.8)	8 (3.1)
HEPATIC FAILURE	0	0	4 (1.7)	0	1 (0.4)	1 (0.4)	0	0	4 (1.6)	0
CUTANEOUS NON-SQUAMOUS CELL CARCINOMA	0	0	3 (1.3)	0	1 (0.4)	0	0	0	3 (1.2)	0
FACIAL PARESIS	1 (0.6)	0	0	0	0	0	0	0	0	0

MedDRA v26.1 coding dictionary applied.
Grouping terms are sorted in descending frequency of Any Grade Phase 3 EC+mFOLFOX6 column.
Cut-off Date: BREAKWATER 22DEC2023
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 30APR2024 (14:57)
Output File: ./C4221015 P3 ORR PCD/ISS SCS ISE SCE 20240319 Unblinded/adae s062 folfox aesi
Table 14.3.1.2.3.103 encorafenib is for Pfizer internal use.

Table 33. Applicant - CRC - Summary of Clinical Safety Summary of Serious Treatment-Emergent AESIs for Encorafenib, by Grouping Terms in Decreasing Frequency of All Grades for Phase 3, Safety Lead-in and POOLED Set (All Causalities) (Protocol C4221015)

Number of Participants Evaluable for AEs	Phase 3 EC (N=154)		Phase 3 EC+mFOLFOX6 (N=231)		Phase 3 Control (N=228)		SLI EC+mFOLFOX6 (N=27)		Pooled EC+mFOLFOX6 (N=258)	
Number (%) of Participants: by GROUPING	Any Grade n (%)	Grade 3 or Higher n (%)	Any Grade n (%)	Grade 3 or Higher n (%)	Any Grade n (%)	Grade 3 or Higher n (%)	Any Grade n (%)	Grade 3 or Higher n (%)	Any Grade n (%)	Grade 3 or Higher n (%)
With Any Adverse Event	0	0	13 (5.6)	12 (5.2)	12 (5.3)	12 (5.3)	2 (7.4)	2 (7.4)	15 (5.8)	14 (5.4)
MYELOSUPRESSION	0	0	10 (4.3)	10 (4.3)	10 (4.4)	10 (4.4)	1 (3.7)	1 (3.7)	11 (4.3)	11 (4.3)
QT PROLONGATION	0	0	2 (0.9)	2 (0.9)	1 (0.4)	1 (0.4)	2 (7.4)	2 (7.4)	4 (1.6)	4 (1.6)
CUTANEOUS NON-SQUAMOUS CELL CARCINOMA	0	0	1 (0.4)	0	0	0	0	0	1 (0.4)	0
HEPATIC FAILURE	0	0	0	0	1 (0.4)	1 (0.4)	0	0	0	0

MedDRA v26.1 coding dictionary applied.
Grouping terms are sorted in descending frequency of Any Grade Phase 3 EC+mFOLFOX6 column.
Cut-off Date: BREAKWATER 22DEC2023
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 30APR2024 (14:57)
Output File: ./C4221015 P3 ORR PCD/ISS SCS ISE SCE 20240319 Unblinded/adae s062 folfox saesi
Table 14.3.1.2.3.107 encorafenib is for Pfizer internal use.

Table 34. Applicant - CRC - Summary of Clinical Safety ADRs for the Combination of EC+mFOLFOX6 by SOC and ADR Terms for Phase 3, Safety Lead-in and POOLED Set (All Causalities) (Protocol C4221015)

Number of Participants Evaluable for AEs	Phase 3 EC (N=154)		Phase 3 EC+mFOLFOX6 (N=231)		Phase 3 Control (N=228)		SLI EC+mFOLFOX6 (N=27)		Pooled EC+mFOLFOX6 (N=258)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
Number (%) of Participants: by SYSTEM ORGAN CLASS and ADR Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	140 (90.9)	34 (22.1)	226 (97.8)	113 (48.9)	209 (91.7)	63 (27.6)	27 (100.0)	16 (59.3)	253 (98.1)	129 (50.0)
Gastrointestinal disorders	82 (53.2)	11 (7.1)	172 (74.5)	21 (9.1)	178 (78.1)	21 (9.2)	25 (92.6)	6 (22.2)	197 (76.4)	27 (10.5)
Nausea	30 (19.5)	1 (0.6)	118 (51.1)	6 (2.6)	110 (48.2)	7 (3.1)	20 (74.1)	0	138 (53.5)	6 (2.3)
Diarrhea	25 (16.2)	2 (1.3)	79 (34.2)	3 (1.3)	107 (46.9)	8 (3.5)	10 (37.0)	2 (7.4)	89 (34.5)	5 (1.9)
Vomiting	20 (13.0)	1 (0.6)	77 (33.3)	8 (3.5)	48 (21.1)	5 (2.2)	11 (40.7)	1 (3.7)	88 (34.1)	9 (3.5)
ABDOMINAL PAIN	43 (27.9)	7 (4.5)	61 (26.4)	8 (3.5)	62 (27.2)	3 (1.3)	11 (40.7)	2 (7.4)	72 (27.9)	10 (3.9)
Constipation	21 (13.6)	1 (0.6)	47 (20.3)	1 (0.4)	44 (19.3)	1 (0.4)	7 (25.9)	0	54 (20.9)	1 (0.4)
PANCREATITIS	0	0	1 (0.4)	1 (0.4)	2 (0.9)	1 (0.4)	1 (3.7)	1 (3.7)	2 (0.8)	2 (0.8)
Skin and subcutaneous tissue disorders	100 (64.9)	2 (1.3)	154 (66.7)	4 (1.7)	43 (18.9)	1 (0.4)	16 (59.3)	2 (7.4)	170 (65.9)	6 (2.3)
RASH	43 (27.9)	0	71 (30.7)	2 (0.9)	8 (3.5)	0	12 (44.4)	0	83 (32.2)	2 (0.8)
Alopecia	12 (7.8)	0	49 (21.2)	0	23 (10.1)	0	2 (7.4)	0	51 (19.8)	0

Table 34. Applicant - CRC - Summary of Clinical Safety ADRs for the Combination of EC+mFOLFOX6 by SOC and ADR Terms for Phase 3, Safety Lead-in and POOLED Set (All Causalities) (Protocol C4221015)

Number of Participants Evaluable for AEs	Phase 3 EC (N=154)		Phase 3 EC+mFOLFOX6 (N=231)		Phase 3 Control (N=228)		SLI EC+mFOLFOX6 (N=27)		Pooled EC+mFOLFOX6 (N=258)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
Number (%) of Participants: by SYSTEM ORGAN CLASS and ADR Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
DRY SKIN	26 (16.9)	2 (1.3)	40 (17.3)	0	9 (3.9)	0	4 (14.8)	1 (3.7)	44 (17.1)	1 (0.4)
DERMATITIS ACNEIFORM	33 (21.4)	0	39 (16.9)	2 (0.9)	2 (0.9)	0	7 (25.9)	0	46 (17.8)	2 (0.8)
Skin hyperpigmentation	19 (12.3)	0	39 (16.9)	0	5 (2.2)	0	2 (7.4)	0	41 (15.9)	0
PRURITUS	27 (17.5)	0	25 (10.8)	0	6 (2.6)	1 (0.4)	4 (14.8)	0	29 (11.2)	0
HYPERKERATOSIS	6 (3.9)	0	7 (3.0)	0	1 (0.4)	0	4 (14.8)	1 (3.7)	11 (4.3)	1 (0.4)
Nervous system disorders	28 (18.2)	1 (0.6)	149 (64.5)	35 (15.2)	124 (54.4)	14 (6.1)	16 (59.3)	3 (11.1)	165 (64.0)	38 (14.7)
NEUROPATHY PERIPHERAL	5 (3.2)	0	143 (61.9)	34 (14.7)	121 (53.1)	14 (6.1)	16 (59.3)	3 (11.1)	159 (61.6)	37 (14.3)
HEADACHE	23 (14.9)	1 (0.6)	29 (12.6)	1 (0.4)	17 (7.5)	0	4 (14.8)	0	33 (12.8)	1 (0.4)
General disorders and administration site conditions	70 (45.5)	5 (3.2)	148 (64.1)	18 (7.8)	103 (45.2)	10 (4.4)	22 (81.5)	1 (3.7)	170 (65.9)	19 (7.4)
FATIGUE	57 (37.0)	3 (1.9)	114 (49.4)	15 (6.5)	86 (37.7)	9 (3.9)	16 (59.3)	0	130 (50.4)	15 (5.8)
PYREXIA	25 (16.2)	2 (1.3)	61 (26.4)	4 (1.7)	31 (13.6)	1 (0.4)	14 (51.9)	1 (3.7)	75 (29.1)	5 (1.9)
Blood and lymphatic system disorders	31 (20.1)	10 (6.5)	88 (38.1)	25 (10.8)	58 (25.4)	8 (3.5)	7 (25.9)	2 (7.4)	95 (36.8)	27 (10.5)

Table 34. Applicant - CRC - Summary of Clinical Safety ADRs for the Combination of EC+mFOLFOX6 by SOC and ADR Terms for Phase 3, Safety Lead-in and POOLED Set (All Causalities) (Protocol C4221015)

Number of Participants Evaluable for AEs	Phase 3 EC (N=154)		Phase 3 EC+mFOLFOX6 (N=231)		Phase 3 Control (N=228)		SLI EC+mFOLFOX6 (N=27)		Pooled EC+mFOLFOX6 (N=258)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
Number (%) of Participants: by SYSTEM ORGAN CLASS and ADR Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ANEMIA	31 (20.1)	10 (6.5)	88 (38.1)	25 (10.8)	58 (25.4)	8 (3.5)	7 (25.9)	2 (7.4)	95 (36.8)	27 (10.5)
Musculoskeletal and connective tissue disorders	72 (46.8)	1 (0.6)	81 (35.1)	3 (1.3)	23 (10.1)	1 (0.4)	12 (44.4)	0	93 (36.0)	3 (1.2)
ARTHRALGIA	53 (34.4)	1 (0.6)	53 (22.9)	2 (0.9)	8 (3.5)	0	8 (29.6)	0	61 (23.6)	2 (0.8)
MYOPATHY	38 (24.7)	0	33 (14.3)	0	16 (7.0)	1 (0.4)	6 (22.2)	0	39 (15.1)	0
PAIN IN EXTREMITY	9 (5.8)	0	18 (7.8)	1 (0.4)	6 (2.6)	0	3 (11.1)	0	21 (8.1)	1 (0.4)
Metabolism and nutrition disorders	23 (14.9)	0	77 (33.3)	5 (2.2)	57 (25.0)	3 (1.3)	8 (29.6)	0	85 (32.9)	5 (1.9)
Decreased appetite	23 (14.9)	0	77 (33.3)	5 (2.2)	57 (25.0)	3 (1.3)	8 (29.6)	0	85 (32.9)	5 (1.9)
Vascular disorders	27 (17.5)	3 (1.9)	69 (29.9)	6 (2.6)	41 (18.0)	2 (0.9)	8 (29.6)	0	77 (29.8)	6 (2.3)
HEMORRHAGE	27 (17.5)	3 (1.9)	69 (29.9)	6 (2.6)	41 (18.0)	2 (0.9)	8 (29.6)	0	77 (29.8)	6 (2.3)
Investigations	10 (6.5)	5 (3.2)	46 (19.9)	34 (14.7)	22 (9.6)	12 (5.3)	8 (29.6)	8 (29.6)	54 (20.9)	42 (16.3)
Lipase increased	10 (6.5)	5 (3.2)	46 (19.9)	34 (14.7)	22 (9.6)	12 (5.3)	8 (29.6)	8 (29.6)	54 (20.9)	42 (16.3)
Psychiatric disorders	13 (8.4)	0	24 (10.4)	0	16 (7.0)	0	2 (7.4)	0	26 (10.1)	0
INSOMNIA	13 (8.4)	0	24 (10.4)	0	16 (7.0)	0	2 (7.4)	0	26 (10.1)	0
Immune system disorders	5 (3.2)	1 (0.6)	18 (7.8)	4 (1.7)	14 (6.1)	5 (2.2)	5 (18.5)	1 (3.7)	23 (8.9)	5 (1.9)

Table 34. Applicant - CRC - Summary of Clinical Safety ADRs for the Combination of EC+mFOLFOX6 by SOC and ADR Terms for Phase 3, Safety Lead-in and POOLED Set (All Causalities) (Protocol C4221015)

Number of Participants Evaluable for AEs	Phase 3 EC (N=154)		Phase 3 EC+mFOLFOX6 (N=231)		Phase 3 Control (N=228)		SLI EC+mFOLFOX6 (N=27)		Pooled EC+mFOLFOX6 (N=258)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
Number (%) of Participants: by SYSTEM ORGAN CLASS and ADR Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
DRUG HYPERSENSITIVITY	5 (3.2)	1 (0.6)	18 (7.8)	4 (1.7)	14 (6.1)	5 (2.2)	5 (18.5)	1 (3.7)	23 (8.9)	5 (1.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	32 (20.8)	0	17 (7.4)	2 (0.9)	1 (0.4)	0	3 (11.1)	1 (3.7)	20 (7.8)	3 (1.2)
Melanocytic naevus	20 (13.0)	0	10 (4.3)	1 (0.4)	0	0	2 (7.4)	0	12 (4.7)	1 (0.4)
SKIN PAPILLOMA	13 (8.4)	0	6 (2.6)	0	1 (0.4)	0	0	0	6 (2.3)	0
MALIGNANT MELANOMA	1 (0.6)	0	1 (0.4)	1 (0.4)	0	0	1 (3.7)	1 (3.7)	2 (0.8)	2 (0.8)
SQUAMOUS CELL CARCINOMA OF SKIN	2 (1.3)	0	1 (0.4)	0	0	0	0	0	1 (0.4)	0

MedDRA v26.1 coding dictionary applied.
SOC and ADR terms are sorted in descending frequency of Any Grade Phase 3 EC+mFOLFOX6 column.
ABDOMINAL PAIN includes PTs of Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort, Hepatic pain, Pelvic pain
ANEMIA includes PTs of Anaemia, Anaemia of chronic disease, Anaemia vitamin B12 deficiency, Blood iron decreased, Haematocrit decreased, Haemoglobin decreased, Iron deficiency anaemia, Red blood cell count decreased
ARTHRALGIA includes PTs of Arthralgia, Joint stiffness, Musculoskeletal pain
DERMATITIS ACNEIFORM includes PTs of Acne, Dermatitis acneiform
DRUG HYPERSENSITIVITY includes PTs of Anaphylactic reaction, Anaphylactic shock, Drug hypersensitivity, Hypersensitivity, Urticaria
DRY SKIN includes PTs of Dry skin, Skin fissures, Xeroderma, Xerosis
FATIGUE includes PTs of Asthenia, Fatigue, Lethargy
HEADACHE includes PTs of Headache
HEMORRHAGE includes PTs of Anal haemorrhage, Catheter site haemorrhage, Conjunctival haemorrhage, Epistaxis, Gastric haemorrhage, Gastrointestinal haemorrhage, Gingival bleeding, Haematochezia, Haematoma, Haematuria, Haemoptysis, Haemorrhoidal haemorrhage, Heavy menstrual bleeding, Intermenstrual bleeding, Lower gastrointestinal haemorrhage, Melaena, Naevus haemorrhage, Occult blood, Orbital haematoma, Post procedural haemorrhage, Postmenopausal haemorrhage, Rectal haemorrhage, Stoma site haemorrhage, Subdural haematoma, Tumour haemorrhage, Umbilical haemorrhage, Upper gastrointestinal
haemorrhage, Uterine haemorrhage, Vaginal haemorrhage
HYPERKERATOSIS includes PTs of Hyperkeratosis, Keratosis pilaris, Seborrhoeic keratosis
INSOMNIA includes PTs of Insomnia, Middle insomnia, Sleep disorder
MALIGNANT MELANOMA includes PTs of Malignant melanoma, Malignant melanoma in situ
MYOPATHY includes PTs of Muscle contracture, Muscle disorder, Muscle spasms, Muscular weakness, Musculoskeletal chest pain, Musculoskeletal discomfort, Myalgia, Myositis
NEUROPATHY PERIPHERAL includes PTs of Cold dysaesthesia, Dysaesthesia, Hyperaesthesia, Hypoaesthesia, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral motor neuropathy, Peripheral sensory neuropathy, Polyneuropathy
PAIN IN EXTREMITY includes PTs of Limb discomfort, Pain in extremity
PANCREATITIS includes PTs of Pancreatitis, Pancreatitis acute
PRURITUS includes PTs of Anal pruritus, Eye pruritus, Pruritus, Vulvovaginal pruritus
PYREXIA includes PTs of Body temperature increased, Pyrexia
RASH includes PTs of Eyelid rash, Nodular rash, Perineal rash, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular
SKIN PAPILLOMA includes PTs of Papilloma, Skin papilloma
SQUAMOUS CELL CARCINOMA OF SKIN includes PTs of Keratoacanthoma
Cut-off Date: BREAKWATER 22DEC2023
PFIZER CONFIDENTIAL Source Data: adae Table Generation: 30APR2024 (14:51)
Output File: ./C4221015 P3 ORR PCD/ISS_SCS_ISE_SCE_20240319_Unblinded/adae_s062_folfox_adr
Table 14.3.1.2.2.102 encorafenib is for Pfizer internal use.

APPEARS THIS WAY ON ORIGINAL

SUMMARY AND CONCLUSIONS

8.3. **Statistical Issues**

The FDA's Assessment:
The statistical review of this application was based on the efficacy evaluation of the BREAKWATER study, a randomized (multicenter, open label, Phase 3) study comparing encorafenib combination with cetuximab and mFOLFOX6 to standard-of-care first-line chemotherapy. The primary efficacy comparison of ORR as assessed by BICR was statistically significant, with a rate of 60.9% [95% CI: 51.6, 69.5] in the EC+mFOLFOX6 arm compared to 40.0% [95% CI: 31.3, 49.3] in the control arm (p-value = 0.0008). The responses in the EC+mFOLFOX arm had a median DOR by BICR of 13.9 months [95% CI: 8.5, NE]. The key secondary endpoint of OS was not mature (37.7% of the deaths required for the final analysis observed), with a positive trend observed (HR=0.47 [95% CI: 0.32, 0.69]). At this data cutoff of BREAKWATER study, no analyses of the co-primary endpoint of PFS were conducted.

There were no major statistical issues in the review of this application. Although there is variability in the ORR observed for different control choices, it should be noted that because the control treatment is chosen by the investigator and may be correlated with the patient characteristics, this study is not designed to address the difference between control arm therapies.

8.4. **Conclusions and Recommendations**

The FDA's Assessment:
FDA concludes that the results of the BREAKWATER trial demonstrate that encorafenib in combination with cetuximab and mFOLFOX6 provides a statistically significant and clinically meaningful improvement in BICR-ORR in patients with mCRC with a *BRAF V600E* mutation who were randomized to receive encorafenib in combination with cetuximab and mFOLFOX6 compared to patients who received standard-of-care first-line chemotherapy with either mFOLFOX6, FOLFOXIRI, or CAPOX each with or without bevacizumab. ORR has been used as a primary endpoint to assess efficacy and to support accelerated approval in some disease settings and is an acceptable endpoint to demonstrate the effectiveness of encorafenib for the proposed indication. The safety profile of encorafenib administered at a dose of 300 mg orally once daily in combination with cetuximab and mFOLFOX6is acceptable in the context of treatment of patients with a serious and life-threatening condition and is manageable with guidelines provided in product labeling. Although the study was not designed to individually assess the EC+mFOLFOX6 regimen versus each of the three chemotherapy regimens (and the response appears to be higher with FOLFOXIRI), the overall effect is considered sufficient for the approval recommendation. Importantly FOLFOXIRI is only administered to fit patients and is uncommonly used in the US (mFOLFOXIRI may be used; however, less data are available to support this specific regimen). Because doublet therapy (generally with a bevacizumab product) remains standard for many patients in the US, the overall comparison of EC+ FOLFOX versus investigator's choice therapy was considered acceptable.

The review team recommends granting accelerated approval. A PMR for a confirmatory study will be issued with the approval of this sNDA. The Applicant will provide the results of the PFS analysis from BREAKWATER to verify and describe the clinical benefit of encorafenib in combination with cetuximab and mFOLFOX6 for the treatment of patients with mCRC with a *BRAF V600E* mutation. The BREAKWATER trial is fully enrolled, and the PFS analysis is anticipated in May of 2025.

8.4.1. **Approach to Substantial Evidence of Effectiveness**

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication

   BRAFTOVI is indicated, in combination with cetuximab and mFOLFOX6, for the treatment of patients with metastatic colorectal cancer (mCRC) with a *BRAF V600E mutation*, as detected by an FDA-approved test

   This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR

   c. ☐ Evidence that supported SEE from a prior approval *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[2]

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)
[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)
[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

Primary Statistical Reviewer	Statistical Team Leader
X	X

Primary Clinical Efficacy Reviewer	Primary Clinical Safety Reviewer
Steven Cunningham, MD	Olga Souprountchouk
X	X

Clinical Team Leader
Jamie Brewer, MD

X

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
The Division did not refer the application to the Oncologic Drug Advisory Committee (ODAC) or seek input from Special Government Employees (SGEs) for this supplemental NDA as no significant review issues were identified during the review of this application.

10. Pediatrics

The Applicant's Position:
The safety and effectiveness of encorafenib has not been established in pediatric patients.

The FDA's Assessment:
The Applicant was granted a full waiver of the requirement to conduct pediatric studies under PREA for encorafenib in combination with cetuximab and mFOLFOX6 based on necessary trials being impossible or highly impracticable due to the rarity of this indication in the pediatric population.

11. Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
1.2 Indications and Usage	BRAFTOVI is a kinase inhibitor indicated, in combination with cetuximab and mFOLFOX6, for the treatment of patients with metastatic CRC with a BRAF V600E mutation, as detected by an FDA-approved test.	FDA agrees.
2.1 Patient Selection	*BRAF V600E* Mutation-Positive Metastatic Colorectal Cancer (CRC) Confirm the presence of a *BRAF V600E* mutation in (b) (4) prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (14.3)]*. If no mutation is detected in a plasma specimen, test tumor tissue. Information on FDA-approved tests for the detection of *BRAF*	FDA agrees; minor revision to first sentence: Confirm the presence of a *BRAF V600E* mutation in plasma or tumor tissue prior to initiating BRAFTOVI *[see Warnings and*

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
	V600E mutations in CRC is available at: http://www.fda.gov/CcompanionDiagnostics.	*Precautions (5.2), Clinical Studies (14.2, 14.3)]*. If no mutation is detected in a plasma specimen, test tumor tissue.
2.3 Recommended dosage for BRAF V600E mutation-positive metastatic colorectal cancer	(b) (4)	Edited to include frequency only in 2.3 and cross-references to Clinical Studies sections.
5.Warnings and Precautions	Safety information for BREAKWATER added to subsections 5.1, 5.4, 5.5, 5.7	FDA agrees
6. Adverse Reactions	Safety information added from BREAKWATER.	FDA agrees with minor modifications.
14. Clinical Studies	Efficacy information added from BREAKWATER.	FDA agrees; Additional demographics for race and ethnicity included.

12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure the safe and effective use of encorafenib in combination with cetuximab and mFOLFOX6 for the indicated population given the consistency of the safety profile of the combination regimen with the safety profile observed for encorafenib and cetuximab and mFOLFOX6 separately. In addition, the medical community has experience with the management of adverse reactions observed with this regimen. Recommendations for the safe and effective use of encorafenib in combination with cetuximab and mFOLFOX6 are provided in the US prescribing information as well as in the patient medication guide.

13. Postmarketing Requirements and Commitment

The FDA's Assessment:
The FDA review team recommends the following postmarketing requirement:

PMR 4753-1

Conduct a randomized comparative clinical trial intended to verify and describe the clinical benefit of encorafenib and cetuximab in combination with mFOLFOX6 in adult patients with previously untreated *BRAF* V600E mutation-positive metastatic colorectal cancer by assessing PFS. Data for this may be obtained from the ongoing clinical trial, BREAKWATER (C4221015), "An Open-Label, Multicenter, Randomized Phase 3 Study of EC Alone (EC Arm) Or In Combination With Chemotherapy (mFOLFOX6; EC + mFOLFOX6 Arm) Versus Standard-of-Care Chemotherapies (Control Arm: mFOLFOX6, FOLFOXIRI, or CAPOX Each With or Without Bevacizumab) in First-Line Participants With *BRAF V600E*-Mutant mCRC."

]

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	X__ Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes X__ No
□	Other considerations (e.g.: PK/Pharmacodynamics), if applicable:	__ Yes __ No

14. Division Director (DHOT) (NME ONLY)

X

15. Division Director (OCP)

X

16. Division Director (OB)

X

17. Division Director (Clinical)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

I agree with the review teams' approval recommendations (granting accelerated approval). The Applicant submitted data from the BREAKWATER trial of encorafenib in combination with cetuximab and mFOLFOX6 for the treatment of adult patients with metastatic CRC with a BRAF V600E mutation. The BREAKWATER trial was a randomized, active-controlled, open-label study designed to compare the efficacy of EC + mFOLFOX to (investigator's choice of) standard-of-care chemotherapy, which included mFOLFOX6, FOLFOXIRI, or CAPOX each with or without bevacizumab. The statistically significant effect on ORR per RECIST v1.1 as assessed by BICR was 61% [95% CI: 51.6, 69.5] for the EC + mFOLFOX6 Arm and 40% [95% CI: 31.3, 49.3] for the Control Arm. This effect is reasonably likely to predict for clinical benefit also noting the favorable trend in OS described in the efficacy section of this review.

To support regular approval, the applicant proposed do submit the final results of the BREAKWATER trial. The study is fully enrolled, and an efficacy supplement is expected in the 2025 calendar year.

X _____

18. Appendices

18.1. References

The Applicant's References:

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18.2. **Financial Disclosure**

The FDA's Assessment:

See FDA discussion of financial disclosure in Section 8.1.

The Applicant's Position:
Study C4221015 is considered to be covered by the "Financial Disclosure for Clinical Investigators" regulation. All investigators were assessed for equity interest, significant payments of other sorts, proprietary interest, and other compensation. As this study is still ongoing, financial disclosure information summarized here may change or be updated prior to study closure. The documentation collected and presented here is current as of 12 April 2024.

Of the 1,709 clinical investigators in Study C4221015, certification is provided for 1,708 (99.9%) of the investigators. Due diligence activities were required for 4 clinical investigators. One (1) of the 1,709 (0.09%) clinical investigators in this study had financial interests to disclose. During the conduct of this trial, including the processing, analyzing and reporting of data, Pfizer applied procedures designed to minimize the potential of bias in the data. No concerns were raised regarding the overall integrity of the data.

Covered Clinical Study (Name and/or Number): C4221015 (BREAKWATER)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1,709		
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): 1		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
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) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

18.3. **Nonclinical Pharmacology/Toxicology**

Data:
Not applicable.
The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees with the Applicant's position.

18.4. **OCP Appendices (Technical documents supporting OCP recommendations)**

18.4.1. **Population PK Analysis**

Executive Summary:

- The popPK model of encorafenib was developed for participants with BRAF V600E-mutated mCRC in BREAKWATER, based on a previously established PopPK model using data from nine trials of encorafenib.

- The PK of encorafenib, administered in combination with cetuximab and mFOLFOX6, were well described using a two-compartment model with first-order absorption and concentration-dependent auto-induction component.
- Based on the intrinsic and extrinsic factors evaluated in the current PopPK model, no dosage modifications are recommended. The encorafenib exposures observed in BREAKWATER are comparable to historical data at the same dosage. The currently labeled encorafenib dosing regimen for BRAF V600E-mutant mCRC (300 mg QD) is considered appropriate for the current submission.

Background:

Encorafenib (BRAFTOVI) is a kinase inhibitor that targets BRAF V600E, as well as wild-type BRAF and CRAF. Cetuximab (ERBITUX) is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR). The mFOLFOX regimen consists of oxaliplatin, leucovorin, and FU. The purpose of the current supplemental NDA (efficacy) submission is to seek accelerated approval for encorafenib (300 mg QD PO) in combination with cetuximab and mFOLFOX6 for the treatment of patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test.

Objectives:

- To describe the PopPK of encorafenib in healthy participants and participants with BRAF V600E-mutant mCRC from nine trials
- To evaluate potential covariates in the PopPK model, including tumor type and drugs given in combination
- To evaluate the predictive performance of the global model for the encorafenib PopPK for participants with metastatic colorectal cancer (mCRC) in BREAKWATER

Data:

Table 35. Summary of Participant Categorical Characteristics for the PopPK Model

Variable	Protocol	ARRAY-162-105	C4221001	C4221004	C4221005	C4221006	C4221008	C4221009	C4221010	C4221013	Total
Combination Drug	None	15 (100%)	0 (0%)	275 (38%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	82 (100%)	0 (0%)	372 (28%)
	Binimetinib	0 (0%)	0 (0%)	449 (62%)	74 (100%)	13 (100%)	98 (100%)	0 (0%)	0 (0%)	55 (73%)	689 (53%)
	Other	0 (0%)	62 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	167 (100%)	0 (0%)	20 (27%)	249 (19%)
CYP3A Inducer	Absence or Weak	15 (100%)	62 (100%)	718 (99%)	73 (99%)	13 (100%)	98 (100%)	167 (100%)	80 (98%)	75 (100%)	1301 (99%)
	Strong	0 (0%)	0 (0%)	6 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	9 (1%)
CYP3A Inhibitor	Absence or Weak	15 (100%)	50 (81%)	622 (86%)	59 (80%)	12 (92%)	85 (87%)	128 (77%)	71 (87%)	57 (76%)	1099 (84%)
	Moderate	0 (0%)	11 (18%)	76 (10%)	8 (11%)	0 (0%)	7 (7%)	29 (17%)	7 (9%)	11 (15%)	149 (11%)
	Strong	0 (0%)	1 (2%)	26 (4%)	7 (9%)	1 (8%)	6 (6%)	10 (6%)	4 (5%)	7 (9%)	62 (5%)
Hepatic NCI	0	15 (100%)	39 (63%)	684 (94%)	60 (81%)	10 (77%)	81 (83%)	118 (71%)	71 (87%)	58 (77%)	1136 (87%)
	1	0 (0%)	22 (35%)	38 (5%)	14 (19%)	3 (23%)	7 (7%)	47 (28%)	11 (13%)	16 (21%)	158 (12%)
	2	0 (0%)	0 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	4 (0%)
	Missing	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	10 (10%)	1 (1%)	0 (0%)	0 (0%)	12 (1%)

Source: Table 5. PMAR-EQDD-C422f-sNDA-1564 POPULATION MODELING ANALYSIS REPORT

Methods:

The analyses were conducted using nonlinear mixed-effects modeling methodology as implemented in NONMEM version 7.5.0 (ICON Development Solutions, Ellicott City, MD) for predictive checks and covariate testing. R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) was utilized for graphics, additional statistical analyses, diagnostics, and data manipulation.

Results:

This PopPK analysis of encorafenib was performed using data from 1,310 participants who received encorafenib, as monotherapy or in combination with other drugs, from 9 trials. Overall, 716 (55%) were male, 1,178 (90%) were White, the median (range) baseline age was 58 years old (19-94 years) and the median (range) baseline body weight was 76 kg (34-168 kg). Summary statistics for categorical and continuous demographic variables are presented in **Table 35.** Summary of Participant Categorical Characteristics for the PopPK Model.

A two-compartment model with first-order absorption and elimination reasonably characterized the concentration-time profile of encorafenib PK in participants with BRAF V600E-mutant mCRC from BREAKWATER (**Table 36**). An encorafenib concentration-dependent E_{max} function successfully described the time-varying net auto-induction of encorafenib. The analysis included 1,714 observations from 373 participants who received EC with or without mFOLFOX6 in BREAKWATER. Fixed and random effects for the final model were estimated using data from nine clinical studies, and post-hoc parameter estimates were derived for

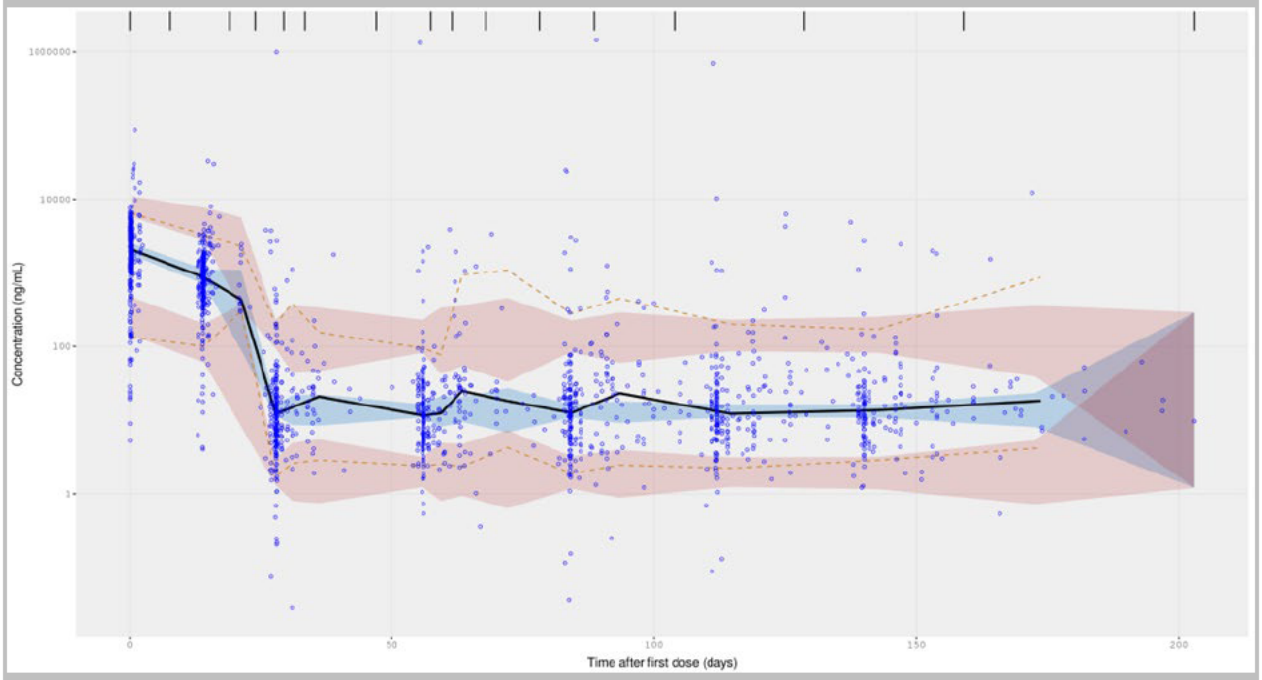
BREAKWATER participants using this model.

Table 36. PopPK Final Model Parameter Estimation

Parameter	Estimate	RSE %
KA - oral Absorption rate constant	0.954	5.7%
CL/F [L/h]	12.2	3.5%
V2/F - Central volume of distribution [L]	61.7	3.6%
Q/F – Inter-compartmental clearance [L/h]	1.05	5.5%
V3/F - Periph volume of distribution [L]	54.5	20%
turnover half-life for enzyme	64.3	13.4%
EMAX	1.86	7%
EC50 CP=0	9.1	8.5%
GAM	10 FIXED	
W- prop residual error	0.589	1.3%
CLTUM21	-0.175	20.5%
CLTUM22	-0.0938	46.3%
V2BWT1	0.588	15.2%
CLAGE1	-0.326	21.8%
IIV on Ka	0.5	--
IIV on CL/F	0.57	--
IIV on V/F	0.5	--

Source: Reviewer's Analysis

Figure 3. VPC for Encorafenib for BREAKWATER Using Parameters from Final PopPK Model



Source: Figure S1. PMAR-EQDD-C422f-sNDA-1564 POPULATION MODELING ANALYSIS REPORT

The typical value for encorafenib CL/F was 12 L/h on Day 1 vs 35 L/h at steady state, likely due to net autoinduction following multiple dosing. The typical value of V2/F was 62 L. All model parameters were estimated with good precision and were consistent with previously published values. GOF plots and VPC plots demonstrated that the final model adequately characterized the encorafenib plasma concentration–time profiles for the nine studies included in the model. Additional VPC plot confirmed that the final model adequately characterized the encorafenib plasma concentration-time profiles observed in BREAKWATER (**Figure 3**).

Covariate modeling identified three significant covariates for CL/F: age, mCRC tumor type (compared to the reference melanoma population), and other tumor types (compared to the reference melanoma population). Body weight was found to be a (nominally) statistically significant covariate for V2/F. The analysis showed that baseline eGFR (25.8 to 1200 mL/min/1.73 m^2) was not a significant covariate for encorafenib oral clearance, suggesting that renal impairment is not expected to substantially affect encorafenib plasma exposure. This finding aligns with prior population PK modeling results. Similarly, baseline AST and baseline total bilirubin were not significant covariates for encorafenib clearance, indicating that plasma exposure is not expected to be affected by mild hepatic impairment (n=153). This is also consistent with previous PK modeling, which showed no clinically significant differences in encorafenib PK with mild hepatic impairment.

None of the intrinsic or extrinsic factors evaluated, including sex, total plasma protein, albumin,

LDH, combination treatment, or ECOG performance status, had a significant impact on encorafenib oral clearance.

Based on this PopPK analysis, age, mCRC tumor type, other tumor types, and body weight were (nominally) statistically significant predictors of encorafenib plasma exposure. However, the predicted changes in PK parameters based on these factors were estimated to be less than 20%, and therefore not considered clinically significant. No dosage modifications are recommended based on the intrinsic or extrinsic factors evaluated.

The final population PK model for encorafenib was deemed adequate for predicting post-hoc encorafenib plasma exposure metrics for BREAKWATER participants, which were subsequently used for ER analyses with efficacy and safety endpoints.

Reviewer's comments:

1. *The reviewer was able to replicate the updated encorafenib PopPK model, and the estimated values were consistent with those submitted by the Applicant.*
2. *The PK of encorafenib, administered alone or in combination with cetuximab and mFOLFOX6, were reasonably described using a 2-compartment model with first-order absorption and elimination along with a concentration-dependent Emax function to account for the time-varying net auto-induction of encorafenib.*
3. *Based on the intrinsic and extrinsic factors evaluated in the current PopPK model, no dose modifications are recommended. Encorafenib exposures observed in BREAKWATER are comparable to historical data at the same dose. The currently labeled encorafenib dosing regimen for mCRC (300 mg QD) is considered appropriate for this submission.*

18.4.2. Exposure-Response Analysis

Exposure Efficacy Analysis:

The efficacy ER analysis evaluated the relationship with the primary efficacy endpoint overall response rate (ORR) based on BICR. The PopPK model-derived encorafenib exposure metrics included in this analysis were C_{max} on Day 1 and at steady state, C_{avg} at steady state (Day 15), and C_{avg} over the first 15 days.

The ER analysis included data from participants who received EC + mFOLFOX6 in the randomized Phase 3 portion of BREAKWATER, with evaluable exposure metrics (N=107) from the subset of patients included in the primary ORR analysis (N=110). No significant efficacy ER relationship between ORR and encorafenib exposure was identified, and no covariate effects were observed.

Exposure Safety Analysis:

In exploring the relationship between encorafenib plasma exposures and selected safety endpoints, data from 373 participants enrolled in BREAKWATER were analyzed. This included 27 participants from the safety-lead in portion who received EC + mFOLFOX6 t, 149 participants who received EC in the phase 3 portion, and 197 participants who received EC +

mFOLFOX6 in the phase 3 portion. Three safety endpoints were evaluated: (1) all-causality AEs with ≥25% frequency in arms (combined) (i.e., nausea, diarrhea, decreased appetite, vomiting, anemia, and arthralgia), (2) certain adverse events of special interest (AESIs), i.e., Myelosuppression, Cutaneous Non-squamous Cell Carcinoma, Facial Paresis, Hepatic Failure, and QT Prolongation) (3) any Grade 3 or higher AE.

An ER relationship was identified for the encorafenib C_{avg} over the first 15 days and any Grade 3 or higher AE. Binomial logistic regression results indicated that participants with higher C_{avg} over the first 15 days, older age, lower baseline hemoglobin, and concomitant chemotherapy (mFOLFOX6) were more likely to experience a Grade 3 or higher AE. These results are consistent with previous ER analyses conducted in the melanoma and mCRC populations. Given the current labeling for encorafenib already includes detailed guidance for dosage modifications for Grade 3 or 4 AEs for specific AEs, these results support the current recommendations found in approved labeling regarding when dosage modifications are warranted for adverse reactions...

No statistically significant ER relationships were identified between encorafenib exposure and all-grade nausea, diarrhea, decreased appetite, vomiting, anemia, and arthralgia. Additionally, no significant ER relationships were found between encorafenib exposure and all-grade AESIs.

Reviewer's Comments:

1. *The reviewer was able to replicate the ER analyses, and the results were generally consistent with those submitted by the Applicant.*
2. *No significant ER relationship was identified for ORR. However, this result should be taken with caution due to limited data and dose range included in the analysis.*
3. *No significant ER relationships were identified for evaluated safety endpoints based on data from BREAKWATER, which supports the use of encorafenib at 300 mg QD in BRAF V600E-mutant mCRC.*

sNDA 210496.017
Array BioPharma
Prior Approval Efficacy Supplement

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer (Safety)	Olga Souprountchouk	Division of Oncology 3	Section: 8.2	**Select one:** _X_ Authored ___ Approved
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Biostatics Team Lead	Chi Song	Division of Biostatistics V	Sections: 8.1, 8.3	**Select one:** ___ Authored _X_ Approved
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Reviewer, Biostatistics V	Dandan Xu	Division of Biostatistics V	Sections: 8.1, 8.3	**Select one:** _X_ Authored ___ Approved
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Clinical Pharmacology Reviewer	Lily Leu	Office of Clinical Pharmacology/Division of Clinical Pharmacology II	Sections: 6	**Select one:** __X__ Authored ____Approved
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Director, Division of Clinical Pharmacology II	Stacy Shord	Office of Clinical Pharmacology/Division of Clinical Pharmacology II	Sections: 6, 19	**Select one:** X Approved
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Pharmacometrics Reviewer	Da Zhang	Office of Clinical Pharmacology/Division of Pharmacokinetics	Sections: 6, 19	**Select one:** X Authored _Approved
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Associate Director for Labeling (ADL)	Doris Auth	Oncology Center for Excellence	Sections: All	**Select one:** ___Authored _X Approved
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Medical Director /Cross Discipline Team Lead	Jamie Brewer	Division of Oncology 3	Sections: All	**Select one:** X Authored X Approved
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Division Director (Clinical)	Steven Lemery	Division of Oncology 3	Sections: All	**Select one:** X Approved
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/s/

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