Clinical Study ARRAY-818-103; C4221003

An Open-label Phase 1 Study to Evaluate Drug-Drug Interactions of Agents Co-Administered with Encorafenib and Binimetinib in Patients with *BRAF* V600-mutant Unresectable or Metastatic Melanoma or Other Advanced Solid Tumors

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Protocol Synopsis

Title	An Open-label Phase 1 Study to Evaluate Drug-Drug Interactions of Agents Co-Administered with Encorafenib and Binimetinib in Patients with *BRAF* V600-mutant Unresectable or Metastatic Melanoma or Other Advanced Solid Tumors
Protocol Number	ARRAY-818-103; C4221003
Phase	1
Study Center(s)	Approximately 30 centers globally
Objectives	All objectives pertain to the drug-drug interaction (DDI) phase of the study only. **Primary:** • To evaluate the effect of single and multiple oral doses of encorafenib in combination with binimetinib on the single oral dose pharmacokinetics (PK) of the cytochrome P450 (CYP) enzyme probe substrates, losartan (CYP2C9), midazolam (CYP3A4), caffeine (CYP1A2), omeprazole (CYP2C19), and dextromethorphan (CYP2D6) and selected metabolites, in patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors. • To evaluate the effect of single and multiple oral doses of encorafenib in combination with binimetinib on the single oral dose PK of rosuvastatin, an organic anion-transporting polypeptide (OATP) /breast cancer resistance protein (BCRP) substrate, and on the single oral dose PK of bupropion (a CYP2B6 substrate) and hydroxybupropion, in patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors. • To evaluate the effect of multiple doses of modafinil, a moderate CYP3A4 inducer, on the multiple oral dose PK of encorafenib and its metabolite, LHY746, in patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors. **Secondary:** • To assess the single and multiple dose PK of encorafenib, LHY746 and binimetinib (and its metabolite, AR00426032) after coadministration with a single oral dose of the CYP probe cocktail, rosuvastatin, and bupropion.

	• To assess the safety and tolerability of single and multiple oral doses of encorafenib in combination with binimetinib when administered with a single oral dose of the CYP probe cocktail, rosuvastatin and bupropion during the DDI portion of the study. • To assess safety and tolerability of multiple oral doses of encorafenib in combination with binimetinib when administered with multiple doses of modafinil during the DDI portion of the study. CCI [redacted]
Endpoints	**Primary:** • Changes in plasma maximum concentration (C_{max}) and area under the concentration time curve from time zero to the time of last quantifiable concentration (AUC_{last}): midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxy omeprazole, rosuvastatin, bupropion and hydroxybupropion. • Changes in the amount eliminated via urine over an 8-hour period (Ae_{0-8}): losartan and its metabolite (E-3174), dextromethorphan and dextrorphan. • Changes in plasma encorafenib and LHY746 C_{max} and area under the concentration time curve (AUC) in Arm 3. **Secondary:** • Metabolite ratios (MR_{AUC} and MR_{Cmax}) for 1-OH midazolam/midazolam, paraxanthine/caffeine, 5-hydroxy omeprazole/omeprazole, hydroxybupropion/bupropion and LHY746/encorafenib and MR_{Ae0-8} for E-3174/losartan and dextrorphan/dextomethorphan. • Pharmacokinetic parameters (e.g., time to reach C_{max} [T_{max}], AUC from time zero extrapolated to infinity [AUC_{inf}], percent of AUC extrapolated [$AUC_{\%extrap}$], apparent terminal elimination rate constant [Kel], apparent terminal elimination half-life [$T_{1/2}$], apparent total body clearance after extravascular administration [CL/F], and apparent total volume of distribution after extravascular administration [V_z/F]) where calculable, for midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxy omeprazole, rosuvastatin, bupropion and hydroxybupropion.

	• Pharmacokinetic parameters (e.g., urine concentration [C_{urine}], quantity of urine excreted during each collection interval [Vol], cumulative amount excreted in urine during each collection interval [CumA]$_e$, and percentage of dose recovered in urine [Fe] %) for losartan, E-3174, dextromethorphan and dextrorphan. • Pharmacokinetic parameters (e.g., C_{max}, AUC_{last}, T_{max}, AUC_{inf}, $AUC_{\%extrap}$, Kel, $T_{1/2}$, CL/F, and V_z/F) for encorafenib, LHY746, binimetinib and AR00426032 where calculable. • Safety will be evaluated by monitoring adverse events (AEs), physical examinations, ophthalmic examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), echocardiogram (ECHO)/multigated acquisition scan (MUGA), and clinical laboratory tests. CCI [redacted]
Design	This is an open-label, 3-arm, fixed-sequence study. Patients will be assigned to the appropriate treatment arm by the Sponsor study team based on eligibility. Enrollment to Arm 3 will begin once Arm 2 enrollment is complete. The study will have 2 treatment phases, a DDI phase followed by a post-DDI phase for each study arm. <u>DDI Phase:</u> **Arm 1** Twenty patients will be enrolled into Arm 1 (CYP probe cocktail arm). Patients will receive a single oral dose of the CYP probe cocktail (losartan, dextromethorphan, caffeine, omeprazole, and midazolam) on Day -7. Encorafenib, administered once daily (QD) and binimetinib, administered twice daily (BID) will be initiated on Day 1. Patients will then receive a single oral dose of the CYP probe cocktail on Day 1 and Day 14. Blood and urine PK sampling will be conducted from 0 to 8 hours on Day -7, Day 1 and Day 14. **Arm 2** Ten patients will receive a single oral dose of rosuvastatin and bupropion on Day -7. Encorafenib, administered QD and binimetinib, administered BID will be initiated on Day 1. Patients will then receive

	a single oral dose of rosuvastatin and bupropion on Day 1 and Day 14. Blood PK sampling will be conducted from 0 to 8 hours on Day -7, Day 1 and Day 14. **Arm 3** Six to 12 patients will inititate continuous treatment with encorafenib QD and binimetinib BID on Day 1. Patients will then receive continuous treatment of modafinil QD on Day 15 through Day 21. Blood PK sampling will be conducted from 0 to 8 hours on Day 14 and Day 21. PK data will be analysed after the first 6 patients to look for an indication that the moderate inducer is having a significant effect on encorafenib PK. If there is a ≥ 20% change in geometric mean encorafenib AUC then an additional 6 patients will be enrolled to more fully characterize the effect. **All Arms** Patients who discontinue or require a dose reduction of study drug(s), in particular encorafenib, prior to the final sample collection on Day 14 in Arms 1 and 2 or prior to Day 21 in Arm 3 may be considered unevaluable for PK analyses and may be replaced. If a patient misses 3 or more consecutive doses of encorafenib in any arm or 3 or more doses of modafinil in Arm 3 prior to completion of the last PK sampling on Day 14 in Arms 1 and 2 or on Day 21 in Arm 3 due to noncompliance, the patient may remain on treatment but may be replaced if limited data are available from the patient. In addition, patients who miss any dose of study drugs on any of the PK days, or who vomit within 4 hours after dosing on any of the PK days, may be replaced but may remain on treatment. **Safety Analysis** <u>DDI Phase (through Day 28)</u> All safety data will be recorded in the patient's source documents and electronic case report forms (eCRFs). Adverse events including serious adverse events (SAEs), laboratory profiles (hematology, biochemistry, coagulation, cardiac/muscle enzymes, urinalysis), physical examination (including vital signs, ophthalmic and dermatological examinations), Eastern Cooperative Oncology Group (ECOG) performance status (PS) assessment, and cardiac profiles (ECG and MUGA or ECHO), concomitant medications and/or therapies will be recorded.

	Post DDI Phase: If a patient chooses to not continue in the post-DDI phase, the Day 30 Safety Follow-up Visit assessments will still be performed. During the post-DDI phase patients may continue to receive encorafenib/binimetinib combination until disease progression, unacceptable toxicity, withdrawal of consent, pregnancy, significant protocol deviation, lost to follow up, Investigator decision, death, or study termination by Sponsor. It is recommended that safety evaluations occur every 3 to 4 weeks, unless otherwise specified. Safety should be monitored by assessing physical examination, hematology and chemistry laboratory testing and any other pertinent testing required as part of the safety profile of the compound (dermatological examinations, ophthalmic exams, cardiac profiles) until discontinuation. Adverse events will be collected at every visit. Investigators will be required to record all Grade 3 or 4 AEs. All SAEs are to be reported to the Sponsor or designee using the SAE form. This study does not formally assess efficacy, however, some efficacy assessment is necessary for the Investigator to assess continued benefit. The Sponsor recommends assessing efficacy every 8 to 12 weeks.
Treatment Regimens	Treatments are described as follows: Encorafenib/binimetinib (continuous daily dosing starting on Day 1 for all arms): 450 mg (6 x 75 mg) encorafenib oral capsules QD 45 mg (3 x 15 mg) binimetinib oral tablet BID CYP Probe Cocktail (once on Day -7, Day 1 and Day 14 for Arm 1 only) taken in the following order: 25 mg losartan oral tablet 30 mg dextromethorphan oral capsule 50 mg caffeine as oral liquid 20 mg omeprazole oral capsule 2 mg midazolam as oral syrup Rosuvastatin and bupropion (once on Day -7, Day 1 and Day 14 for Arm 2 only): 10 mg rosuvastatin oral tablet 75 mg bupropion immediate release (IR) oral tablet

	Modafinil (continuous daily dosing starting on Day 15 through Day 21 for Arm 3 only): 400 mg modafinil as oral tablet(s) QD For each arm, all drugs will be taken within 10 minutes total time.
Study Population	Up to approximately 42 patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors; 20 in Arm 1, 10 in Arm 2 and up to 12 in Arm 3.
Duration of Study Participation	Prescreening: Prescreening evaluations must be performed between Day -57 and Day -36 in Arms 1 and 2 and between Day -50 and Day -29 in Arm 3. Screening: Screening of patients will occur within 28 days prior to the first study drug dose on Day -7 (Day -35 to Day -8, inclusive) in Arms 1 and 2 and prior to the first study drug dose on Day 1 (Day -28 to Day -1, inclusive) in Arm 3. DDI Phase: The duration of the DDI phase in Arms 1 and 2 will be 35 days and will include clinic visits on Day -7, Day 1, Day 14, and Day 28. The duration of the DDI phase will be 28 days in Arm 3 and will include clinic visits on Day 1, Day 14, Day 15, Day 21 and Day 28. Post-DDI Phase: Patients will be followed by the Investigator following standard clinical practice and may continue to receive study treatment until discontinuation criteria are met.
Eligibility Criteria	**Inclusion Criteria** Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study: 1. Signed written informed consent; 2. Male or female patient, age ≥ 18 years; 3. Histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma or unknown primary melanoma American Joint Committee on Cancer (AJCC) Stage IIIB, IIIC or IV; or other *BRAF* V600-mutant advanced solid tumors; 4. Presence of *BRAF* V600E and/or V600K mutation in tumor tissue prior to enrollment, as determined using a local test; 5. Evidence of measurable or non-measurable lesions as detected by radiological or photographic methods according to guidelines based on Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1;

	6. Patient with unresectable locally advanced or metastatic melanoma who has received no prior treatment or progressed on or after prior systemic therapy Note: Prior therapy with a BRAF inhibitor (e.g., vemurafenib, dabrafenib, encorafenib and XL281/BMS-908662) and/or a MEK inhibitor (e.g., trametinib, binimetinib, selumetinib, cobimetinib and refametinib) is permitted except in the regimen immediately prior to study entry. Progression during prior BRAF/MEK inhibitor treatment is not required; 7. Patient with other (non-melanoma) *BRAF* V600E and/or V600K - mutant advanced solid tumors who has progressed on standard therapy or for whom there are no available standard therapies Note: Prior therapy with a BRAF inhibitor and/or a MEK inhibitor is permitted except in the regimen immediately prior to study entry. Progression during prior BRAF/MEK inhibitor treatment is not required; if it occurred, the patient's circumstances (e.g., ≥ 1 year since prior BRAF and/or MEK inhibitor, equivocal progression, refractory to available therapies) must be discussed with the Sponsor prior to enrollment; 8. ECOG PS of 0 or 1; 9. Adequate bone marrow, organ function and laboratory parameters: a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, b. Hemoglobin (Hgb) ≥ 9 g/dL without transfusions, c. Platelets (PLT) ≥ 100 x 10^9/L without transfusions, d. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN); patient with liver metastases ≤ 5 ×ULN, e. Total bilirubin ≤ 2 × ULN, f. Creatinine ≤ 1.5 mg/dL, or calculated creatinine clearance (determined as per Cockcroft-Gault) ≥ 50 mL/min; 10. Able to take oral medications; 11. Patient is deemed by the Investigator to have the initiative and means to be compliant with the protocol (treatment and follow-up); 12. Negative serum beta-human chorionic gonadotropin (β-HCG) test (female patient of childbearing potential only) performed within 72 hours prior to first dose and consent to ongoing urine pregnancy testing during the course of the study; 13. Male patients and female patients of childbearing potential must agree to use an acceptable method of contraception as defined in the study protocol; <u>ARM 1 ONLY:</u> 1. Non-smoker who has not used nicotine containing products for at least 3 months prior to the first dose.

	Exclusion Criteria Patients meeting any of the following criteria are not eligible for enrollment in the study: 1. Symptomatic brain metastasis. Patients previously treated or untreated for these conditions who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable, with imaging (e.g., magnetic resonance imaging [MRI] or computed tomography [CT] demonstrating no current evidence of progressive brain metastases at screening); 2. History of reaction to any of the study medications in the arm the patient is enrolled in this trial; 3. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any herbal medications/supplements or any medications or foods that are moderate or strong inhibitors or inducers of CYP3A4/5; 4. Consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each starting from Day -14 and through the DDI phase (Day 28), due to potential CYP3A4 interaction with the study drugs. Orange juice is allowed; 5. Symptomatic or untreated leptomeningeal disease; 6. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); 7. Clinically significant cardiac disease including any of the following: a. Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2) b. Left ventricular ejection fraction (LVEF) < 50% as determined by MUGA or ECHO c. Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy d. History or presence of clinically significant ventricular arrhythmias or atrial fibrillation e. Clinically significant resting bradycardia f. Unstable angina pectoris ≤ 3 months prior to start of study drug g. Acute myocardial infarction ≤ 3 months prior to start of study drug

	h. QT interval corrected for heart rate using the Fridericia formula (QTcF) > 480 msec at screening; 8. Impaired hepatic function as defined by Child-Pugh class B or C; 9. Impaired gastrointestinal function or disease which may significantly alter the absorption of study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection); 10. Known hyper-coagulability risks other than malignancy (e.g., Factor V Leiden syndrome); 11. Thromboembolic event (e.g. including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli) except catheter-related venous thrombosis ≤ 12 weeks prior to starting study treatment. ***Note:*** Patients with catheter-related thromboembolic events are allowed; 12. Any of the following: a. Nitrosourea or mitomycin-C within 6 weeks prior to start of study drug b. Other chemotherapy, radiation therapy that included > 30% of the bone marrow reserve, or biological therapy (e.g., antibodies) within 4 weeks prior to start of study drug c. Continuous or intermittent small-molecule therapeutics or investigational agents within 5 half-lives of the agent (or within 4 weeks prior to start of study drug, when half-life is unknown) d. Residual Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 side effects of any such therapy (residual Grade 2 alopecia is permitted); 13. Discontinuation of prior BRAF and/or MEK inhibitor treatment due to left ventricular dysfunction, pneumonitis/interstitial lung disease, or retinal vein occlusion; 14. Known positive serology for human immunodeficiency virus (HIV) infection, active hepatitis B and/or active hepatitis C infection; 15. History of Gilbert's syndrome; 16. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgement of the Investigator, would make the patient inappropriate for the study;

	17. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until termination of gestation, confirmed by a positive β-hCG laboratory test (> 5 mIU/mL). ARM 1 ONLY: 1. Positive urine cotinine test at screening; 2. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP3A4, CYP2C9, CYP1A2, or CYP2C19 and any substrates or inhibitors CYP2D6. ARM 2 ONLY: 1. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP2B6 or any substrates or inhibitors of BCRP, OATP1B1 or OATP1B3. ARM 3 ONLY: 1. History of psychosis, depression or mania; 2. History of angioedema; 3. History of mitral valve prolapse; 4. History of left ventricular hypertrophy; 5. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP3A4.
Statistical Considerations	**Sample Size Determination** For Arm 1, sample size was specified based on the substrate in the CYP probe cocktail with the highest reported within patient variability in AUC (Ryu 2007). The coefficient of variation of the difference between 2 AUC_{last} values for the same patient for omeprazole is approximately 38%. Assuming a 2-sided significance level of 0.05 and a power of 0.8, approximately 20 patients would need to be evaluable to detect a difference of 25% in mean AUC_{last} . Additionally, these values are similar to other cocktail studies run in oncology patients (Goh 2010). For Arm 2 , the coefficient of variation of the ratio between 2 rosuvastatin AUC_{last} values for the same patient is approximately 47% (Stopfer 2016). Assuming a 2-sided significance level of 0.05 and a power of 0.8, approximately 10 patients would need to be evaluable to detect a difference of 50% in mean AUC_{last}. Assuming an intrasubject variation of 23% for bupropion AUC_{0-8} (Bosilkovska

2014), there is an 80% probability with 10 subjects that a treatment difference will be detected if the true effect size is 33%.

For Arm 3, assuming an intrasubject variation of 36.4% for encorafenib AUC over the final dosing interval (AUC_{tau}, Clinical Study CMEK162X2110), there is an 80% probability with fixed sample sizes of 6 and 12 subjects that a treatment difference will be detected if the true effect size is 74 and 46%, respectively.

Pharmacokinetic Analysis

Descriptive statistics will be calculated for all analytes by arm and day.

For the primary analysis in Arms 1 and 2, an analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed C_{max} and AUC_{last} of midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxy omeprazole, rosuvastatin, bupropion and hydroxybupropion and the urine losartan, E-3174, dextromethorphan and dextrorphan Ae_{0-8}. For the primary analysis in Arm 3, an ANOVA will be performed on the encorafenib ln-transformed C_{max} and AUC. The ANOVA model will include treatment as fixed effect and patient as the random effect. Each ANOVA will include calculation of the least squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference.

Ratios of LSM will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed parameters. In Arms 1 and 2, these ratios will be expressed as a percentage of Day 1 (test) relative to Day -7 (reference), Day 14 (test) relative to Day 1 (reference) and Day 14 (test) relative to Day -7 (reference). In Arm 3, these ratios will be expressed as a percentage of Day 21 (test) relative to Day 14 (reference).

Consistent with the 2 one-sided test, 90% confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the analyses on the ln-transformed parameters. In Arms 1 and 2, the CIs will be expressed as a percentage of Day 1 (test) relative to Day -7 (reference) and Day 14 (test) relative to Day 1 (reference) and Day 14 (test) relative to Day -7 (reference). In Arm 3, these ratios will be expressed as a percentage of Day 21 (test) relative to Day 14 (reference).

Similarly, an ANOVA will be performed on the ln-transformed MR_{AUC} and MR_{Cmax} calculated for 1-OH midazolam/midazolam, paraxanthine/caffeine, 5-hydroxy omeprazole/omeprazole,

	hydroxybupropion/bupropion and LHY746/encorafenib and MR_{Ae0-8} for E-3174/losartan and dextrorphan/dextomethorphan. CCI [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Definition
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse events of special interest
Ae_{0-8}	changes in the amount eliminated via urine over an 8-hour period
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{last}	concentration time curve from time zero to the time of last quantifiable concentration
AUC_{inf}	concentration time curve from time zero extrapolated to infinity
$AUC_{\%extrap}$	percent of concentration time curve extrapolated
AUC_{tau}	AUC over the final dosing interval (tau)
AV	atrioventricular
BCRP	breast cancer resistance protein
β-HCG	beta-human chorionic gonadotropin
BID	twice daily
BOR	best overall response
BRAF	BRAF proto-oncogene serine-threonine protein kinase
CDK4/6	cyclin-dependent kinase 4/6

Abbreviation or special term	Definition
CI	confidence interval
CK	creatine phosphokinase
CL/F	apparent total body clearance after extravascular administration
CL_R	renal clearance
C_{max}	maximum concentration
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CT SAE	clinical trial serious adverse event
$CumA_e$	cumulative amount excreted in urine during each collection interval
C_{urine}	urine concentration
CT	computed tomography, clinical trial
CTFG	Clinical Trial Facilitation Group
CV	curriculum vitae
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response

Abbreviation or special term	Definition
DUSP6	dual specificity phosphatase 6
EC	ethics committee (includes institutional review board, research ethics board, and institutional ethics committee)
EC_{50}	half maximal response concentration
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
ERK	extracellular regulated signal kinase
ESMO	European Society of Medical Oncology
F	oral bioavailability
FDA	U.S. Food and Drug Administration
Fe%	percentage of dose recovered in urine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
HA	Health Authorities
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HFSR	hand-foot skin reaction
Hgb	hemoglobin

Abbreviation or special term	Definition
HIV	human immunodeficiency virus
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committees
IGF-1R	type 1 insulin-like growth factor receptor
INR	international normalized ratio
IOP	intraocular pressure
IRB	Institutional Review Board
IV	intravenous
KA	keratoacanthoma
Kel	apparent terminal elimination rate constant
KI	inhibitory constant
K_{inact}	rate of enzyme inactivation
KRAS	Kirsten rat sarcoma viral oncogene homolog
LFT	liver function test
LH	luteinizing hormone
LLN	lower limit of normal
LSM	least squares means
LVEF	left ventricular ejection fraction
MAP	mitogen-activated protein
MAPK	MAP kinase
MASCC	Multinational Association of Supportive Care
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Definition
MEK	MAP kinase kinase
MR	metabolite ratio
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NCI	National Cancer Ins
NE	not evaluable
NOAEL	no-observable-adverse-effect level
NRAS	neuroblastoma RAS viral (v-ras) oncogene homolog
NSCLC	non-small cell lung cancer
OAT1	organic anion transporting 1
OAT3	organic anion transporting 3
OATP	organic anion-transporting polypeptide
OATP1B1	organic anion-transporting polypeptide 1B1
OATP1B3	organic anion-transporting polypeptide 1B3
OCT	ocular coherence tomography
OCT2	organic cation transporter 2
ORR	objective response rate
PD	progressive disease
PDE4D	phosphodiesterase 4D
PDF	portable document format
pERK	phosphorylated ERK
PFS	progression-free survival
P-gp	P-glycoprotein

Abbreviation or special term	Definition
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic(s)
PKC	protein kinase C
PLT	platelets
pMEK	phosphorylated MEK
PO	oral
PORCN	porcupine homolog
PPES	palmar-plantar erythrodysaesthesia syndrome
PR	partial response
PS	performance status
PT	preferred term
PVC	premature ventricular contraction
QD	once daily
QTcF	QT interval corrected for heart rate using the Fridericia formula
RAF	murine leukemia viral oncogene homolog
RAS	guanosine triphosphatase protein
RBC	red blood cell(s)
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RPED	retinal pigment epithelial detachment
RVO	retinal vein occlusion
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	statistical analysis plan
SCC	squamous cell carcinoma

Abbreviation or special term	Definition
SD	stable disease
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TdP	Torsade de Pointes
TBili	total bilirubin
T_{max}	time of the maximum concentration
UDP	uridine diphosphate
UGT1A1	UDP-glucuronosyl transferase 1A1
ULN	upper limit of normal
US	United States
Vol	quantity of urine excreted during each collection interval
Vss	volume of distribution at steady state
V_Z/F	apparent total volume of distribution after extravascular administration
WBC	white blood cell(s)

Amendment 7: Protocol Version 8.0

Amendment Rationale

The reasons for this amendment are as follows:

- To change enrollment language to reflect that patients may be enrolled to Arm 3 prior to the completion of Arm 1 enrollment as described in a Protocol Administrative Change Letter dated 14 April 2020. Unlike Arm 1, both Arms 2 and 3 allow smokers and this revision will provide an opportunity for these patients to participate in the trial once Arm 2 is fully enrolled.
- To revise the Adverse Event and Serious Adverse Events Section 10.1 to align with Pfizer standard operating procedures with SAE reporting directly to Pfizer Safety.
- To include a guidance document to address alternative measures that may need to be considered at particular sites/regions due to the ongoing pandemic (Appendix 13: Alternative Measures During Public Emergencies).
- Other changes have been incorporated to align with Pfizer standards.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol. Key changes made in the body of the protocol are reflected in the Protocol Summary.

Section # and Name	Description of Change	Brief Rationale
Sponsor Signature Page Principal Investigator Agreement Page	Sponsor signature page and Principal Investigator Agreement page has been removed from the protocol.	Sponsor signature page and Investigator Signature page will be separate from the protocol to align with Pfizer protocol standards.
Synopsis 4.1.1 DDI Phase 6.2 Allocation to Treatment	Enrollment language has been changed to reflect that patients may be enrolled to Arm 3 prior to the completion of Arm 1 enrollment.	Unlike Arm 1, both Arms 2 and 3 allow smokers and this revision will provide an opportunity for these patients to participate in the trial once Arm 2 is fully enrolled.
5.0 Patient Population	New Reference to Appendix 13 added.	A reference to Appendix 13 was added for guidance for patients with active or presumed SARS CoV-2 infection.
6.5 Dose Modifications and Reductions	New reference to Appendix 13 added.	A reference to Appendix 13 was added for guidance for patients with active or presumed SARS CoV-2 infection.
7.0 Study Procedures and Assessments	New reference to Appendix 13 added.	A reference to Appendix 13 was added for guidance for patients with active or presumed SARS CoV-2 infection.
7.3 Pharmacokinetic Assessments	Added language that during COVID-19 pandemic, sites should proactively contact and discuss challenges with the Pfizer clinician and Pfizer clinical pharmacologist.	Guidance added for patients with active or presumed SARS CoV-2 infection.

Section # and Name	Description of Change	Brief Rationale
8.0 Study Assessments	New reference to Appendix 13 added.	A reference to Appendix 13 was added for guidance for patients with active or presumed SARS CoV-2 infection.
9.1 Treatment Discontinuation for Individual Patients	New paragraph added for patients who withdraw consent. New reference to Appendix 12 added.	New text on patients who withdraw consent has been added to align with Pfizer standard operating procedures. A reference to Appendix 12 was added for guidance for participants with active or presumed SARS CoV2 infection.
10.0 Safety Monitoring: Definitions and Reporting	Section 10 was replaced with language from Pfizer standard operating procedures.	Adverse Events and Serious Adverse Events revised to align with Pfizer standard operating procedures.
13.8.1 Data Sharing	New Section added	Data sharing section added to align with Pfizer standard operating procedures.
Appendix 10. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. Appendix 11. Liver Safety: Suggested Actions and Follow-up Appendix 12. ECG Findings of Potential Clinical Concern Appendix 13. Alternative Measures During Public Emergencies	Added per Pfizer standard operating procedures.	Adverse Events and Serious Adverse Events Appendix 10, 11, and 12 added to align with Pfizer standard operating procedures. The Alternative Measures During Public Emergencies Appendix 13 was added as guidance to be followed during public emergencies, including the COVID-19 pandemic.
Entire document	Grammatical changes were made throughout document.	For clarification purposes.

IRB/IEC/HA

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The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 6: Protocol Version 7.0

Amendment Rationale

The primary reason for this amendment is to incorporate additional safety guidelines and safety monitoring to be consistent with other protocols in the encorafenib and binimetinib development programs.
In addition, as encorafenib is the primary concern for drug interaction, language regarding replacement of patients due to dose discontinuation or dose reduction has been modified. Other changes have also been implemented in order to add clarification to the protocol and are outlined below.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol. All changes made in the body of the protocol are reflected in the Protocol Summary.

- Synopsis

  The synopsis was updated to align with body text in the document.

- Section 4.1.1 DDI Phase

  This section was updated to clarify when a patient would be considered unevaluable for PK, to modify patient replacement language and to clarify when a patient could remain on study following missed doses due to noncompliance.

- Section 5.4.2.1 Prohibited Concomitant Medications

  This section was updated to add a statement regarding prohibited anticancer therapies to be consistent with other protocols in the encorafenib and binimetinib development programs and to add clarification around timing of the caffeine restriction in each Arm.

- Section 5.4.2.2 Permitted Concomitant Medication

  Language has been added regarding initiation of thromboprophylaxis.

- Section 6.5 Dose Modifications and Reductions

  The section was updated to modify patient replacement language.

- Table 5 Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

  Language has been added for QTcF prolongation events regarding correction for electrolyte abnormalities and controlling cardiac risk factors for QT prolongation.

- Table 6 Summary of Clinical Laboratory Tests

  This table was updated to correct a formatting issue that was truncating the list of tests required and to add laboratory tests to be consistent with other protocols in the encorafenib and binimetinib development programs.

- Section 7.1.9 Pregnancy Tests

Additional information has been added regarding timing of urine pregnancy tests and instruction on positive results.

- Section 7.4 Disease Assessments

  Language had been added for clarification that efficacy assessments are required although efficacy is not formally being assessed.

- CCI [redacted]

- Section 8.3.4 Post-DDI Phase

  Language had been added to specify that efficacy assessments are required every 8-12 weeks in order to assess continued benefit.

- Section 8.3.4.2 Every 8-12 Weeks

  Language had been added to specify that efficacy assessments are required every 8-12 weeks in order to assess continued benefit.

- Section 9.2 Replacement of Patients

  This section was updated to clarify when a patient would be considered unevaluable for PK, to modify patient replacement language and to clarify when a patient could remain on study following missed doses due to noncompliance.

- Section 15.0 References
  The section has been updated to include a reference supporting the initiation of thromboprophylaxis.

IRB/IEC/HA

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Amendment 5

Amendment Rationale

The primary protocol revision involves decreasing the caffeine dose to 50 mg in the CYP probe cocktail in Arm 1 of the study. A review of the PK data from the first 3 patients who inadvertently received a lower dose of caffeine (50 mg caffeine administered as 100 mg caffeine citrate), showed adequate bioanalytical quantification at the 50 mg dose level to support the evaluation of the primary objective. Caffeine is thought to be a sufficient probe of CYP1A2 activity even at a 50 mg dose (Bosilkovska et al. 2014; Croft et al. 2012).
Additional changes include modification to the protocol title to more accurately reflect the current design of the study and alignment of the text with the Schedule of Events table with regard to PK sampling. Minor changes for consistency and clarification were also implemented.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol. All changes made in the body of the protocol are reflected in the Protocol Summary.

- Title

  The title has been modified to remove the detail regarding number of Arms in the study and drugs being co-administered to better align with the current study design.

- Synopsis

  The synopsis was updated to align with body text in the document.

- Section 2.6.2 Rationale for Dose Selection

  This section was modified to clarify that the CYP probe cocktail will be administered at the dose closest to, or lower than, the doses referenced in the Inje paper (Ryu 2007). This was done to avoid using a higher dose than needed and to allow the use of agents that are commercially available at the different sites and regions where the study is being conducted.

- Section 4.2.1 Treatment Regimens

  This section was modified to reflect a lower dose of caffeine administered and to remove reference to the mg/mL doses for caffeine and midazolam, as this information is detailed in the pharmacy manual and in order to reduce confusion.

- Section 6.1 Dosing Regimen

  This section was modified to reflect a lower dose of caffeine administered and to remove reference to the mg/mL doses for caffeine and midazolam, as this information is detailed in the pharmacy manual and in order to reduce confusion.

- Section 8.3.2.4 Day 14 and Day 21 at Hours 1 and 3

  This section was added to maintain consistency with Table 8 Schedule of Events – Arm 3.

IRB/IEC/HA

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Amendment 4

Amendment Rationale

The primary reason for amendment 4 is to add a drug-drug interaction assessment of a sensitive CYP2B6 substrate and a moderate CYP3A4 inducer.
Arms 1 and 2 will now be allowed to enroll in parallel rather than sequentially and the non-smoking inclusion criteria has been edited to only apply to patients in Arm 1 to aid patient recruitment. Also, the losartan dose has been lowerd from 50 mg to 25 mg to minimize potential side effects.
In addition, some exclusion criteria and guidelines for safety monitoring during the post-DDI phase have been revised to be consistent with other protocols in the encorafenib and binimetinib development programs.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol. All changes made in the body of the protocol are reflected in the Protocol Summary.

- Synopsis

  The synopsis was updated to align with body text in the document.

- Principal Investigator Agreement

  The section was updated to reflect the current version of the GCP Guidance.

- Section 2.3.2.1 Clinical Pharmacology

  The section was updated to to add the terminal elimination half-life of encorafenib.

- Section 2.5.2.2 Safety

  The section was updated to remove reference to the patient population in the current study being the same as the Phase 3 Study CMEK162B2301.

- Section 2.5.2.3 Efficacy

  The section was revised to include updated results from the pivotal phase 3 study CMEK162B2301.

- Section 2.6.1 Rationale for the Study

  The section was updated to include information on a CYP2B6 substrate and a moderate CYP3A4 inducer and the rationale for the drugs selected (bupropion and modafinil).

- Section 2.6.2 Rationale for Dose Selection

  The section was updated to include information on the rationale for the doses of bupropion and modafinil selected.

- Section 3.1 Study Objectives

  The section was updated to include information on the primary and secondary objectives for the addition of bupropion and modafinil.

- Section 3.2 Study Endpoints

  The section was updated to include information on the primary, secondary CCI [redacted] endpoints for the addition of bupropion and modafinil.

- Section 4.1 Study Design Overview

  The section was updated to include detailed information on the addition of bupropion to Arm 2 of the study and to add a new arm (Arm 3) to test the addition of modafinil to encorafenib/binimetinib administration. Updates were also made to the study schema in Figure 1 to reflect these additions. In addition, language regarding replacement of patients has been changed to reflect that patients may be replaced, but not required to be.

- Section 4.1.1 DDI Phase

  The section was updated to allow parallel enrollment into Arms 1 and 2 versus sequential enrollment.

- Section 4.2 Doses and Schedule of Administration

  The section was updated to include detailed information on the doses and dosing instructions for the addition of bupropion to Arm 2 and modafinil in Arm 3. In addition, language regarding replacement of patients has been changed to reflect that patients may be replaced, but not required to be.

- Section 4.2.1 Treatment Regimens

  The section was updated to lower the losartan tablet strength from 50 mg to 25 mg.

- Section 4.3 Duration of Treatment

  The section was updated to include duration days for Arm 3 of the study.

- Section 5.1 Number of Patients

  The section was updated to reflect the increased number of patients planned for the study due to the addition of Arm 3.

- Section 5.2.1 Inclusion Criteria

  Inclusion criteria 4 was modified to clarify that the presence of *BRAF* mutation is determined by a local test, not an approved test.
  Inclusion criteria 8 was redefined as being required for Arm 1 only.

- Section 5.2.2 Exclusion Criteria

  Exclusion criteria 3 was modified to clarify the days of encorafenib/binimetinib administration and to add CYP2B6 substrates to the list of restricted medications. Criteria was modified for clarity and Arm specific bullets for restricted medications were added.
  Exclusion criteria 10 and 11 replaced the prior thromboembolic criteria for consistency with other Array sponsored protocols
  Exclusion criteria 13 was modified to clarify that only patients with specific toxicities be excluded from participating.
  Exclusion criteria 15 was redefined as being required for Arm 1 only.
  Additional exclusion criteria were added for patients enrolled into Arm 3 of the study due to reported adverse events with modafinil administration.

Exclusion criteria 9b and 9c were added for patients enrolled into Arm 3 of the study due to reported adverse events with modafinil administration.

- Section 5.4.2.1 Prohibited Concomitant Medications

  The section was updated to add CYP2B6 substrates to the list of restricted medications. Criteria was modified for clarity and Arm-specific bullets for restricted medications were added.

- Section 5.4.2.3 Prohibited Concomitant Medication Requiring Caution and/or Action

  The section was updated to include cross-references to the schedule of events for Arm 3 (Table 9). This section was also updated to reflect current program guidelines for concomitant medications.

- Section 6.0 Study Treatment

  Sections 6.1 Dosing Regimen, 6.2 Allocation to Treatment and 6.3 Packaging and Labeling were updated to include detailed information on the doses and dosing instructions for the addition of bupropion to Arm 2 and modafinil in Arm 3. In addition, the table describing packaging and labeling has been removed for consistency with other Array sponsored protocols.

- Section 6.1 Dosing Regimen

  The section was updated to lower the losartan tablet strength from 50 mg to 25 mg.

- Section 6.2 Allocation to Treatment

  The section was updated to add detail regarding parallel enrollment into Arms 1 and 2 versus sequential enrollment.

- Section 6.5 Dose Modifications and Reductions

  The section has been changed to reflect that patients may be replaced, but not required to be, reference to QTcF prolongation following binimetinib administration has been removed and a section for uveitis has been added to the dose modification table (Table 6).

- Section 6.5.1.2 Follow-up Evaluations for Appearance of Keratoacanthoma (KA) and/or Squamous Cell Carcinoma (SCC)

  The section has been revised to include guidance on follow up dermatological examinations to be consistent with other encorafenib protocols.

- Section 7.0 Study Procedures and Assessments

  Sub-sections throughout have been updated to include cross-references to the schedule of events for Arm 3 (Table 9).

- Section 7.1.4 Electrocardiogram

  The section was updated to clarify that predose ECGs should be performed up to 30 minutes before any study drug administration, to give examples of abnormal ECGs to be repeated, to indicate that ECG tracing should be made available if requested, and to clarify that QT interval correction will be done using the Fridericia formula.

- Section 7.1.6 Table 7 Summary of Clinical Laboratory Tests
  The table was updated to remove GGT from the panel of chemistry tests required as it is a nonspecific measure of liver function.
- Section 7.1.8 Dermatologic Examinations
  The section was updated to maintain consistentency with the recommended guidelines for following patients in the encorafenib development program.
- Section 7.2 Pharmacokinetic Assessments

  The section was updated to include the analysis of bupropion and hydroxybupropion and to clarify that analytes quantitated are dependent on study arm.
- CCI [redacted]
- Section 8.0 Schedule of Procedures and Assessments

  Sub-sections throughout have been updated to clarify procedures for Arms 1 and 2, to add procedures and schedule of events for Arm 3 and include cross-references to the schedule of events for Arm 3 (Table 9). Subsection 8.3.4.1 was updated to clarify procedures that are recommended to be performed every 3-4 weeks. Subsection 8.3.4.2 and 8.3.4.3 were added to clarify procedures that are recommended to be performed every 8-12 weeks to be consistent with the recommended guidelines for monitoring patients in the encorafenib and binimetinib development programs.
- Section 9.1 Treatment Discontinuation for Individual Patients

  The section was updated to remove the recommendation that patients missing 3 or more consecutive encorafenib and binimetinib doses should be discontinued.
- Section 9.2 Replacement of Patients

  The section has been changed to reflect that patients may be replaced, but not required to be.
- Section 10.8 Reporting of Serious Adverse Events
  The section has been updated to indicate that safety evaluations are recommended to occur every 3 to 4 weeks, unless otherwise specified.
- Section 11.1.1 Sample Size

  The section has been updated to include sample size rationale for Arm 2 and Arm 3 and to clarify approximately 20 patients would be needed in Arm 1 for concistency in the protocol.

- Section 11.1.2 Safety Analysis

  The section has been updated to reflect the study as 3 arms and to indicate that safety evaluations are recommended to occur every 3 to 4 weeks, unless otherwise specified.
- Section 11.1.3 Pharmacokinetic Analysis

The section has been updated to include details regarding days of analysis, the analysis of bupropion and hydroxybupropion, that modafinil may be analyzed and addition of Arm 3 ANOVA information.

- Section 15.0 References

  The section has been updated to include references supporting the choice and doses of bupropion and modafinil.

IRB/IEC/HA

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Amendment 3

Amendment Rationale

The reason for the current amendment is to permit enrollment of patients who have had prior therapy with a BRAF inhibitor (e.g., vemurafenib, dabrafenib, encorafenib and XL281/BMS-908662) and/or a MEK inhibitor (e.g., trametinib, binimetinib, selumetinib, cobimetinib and refametinib), provided the BRAF inhibitor and/or MEK inhibitor was not in the regimen immediately prior to study entry.
In addition, minor changes for consistency and clarification were implemented.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol. All changes made in the body of the protocol are reflected in the Protocol Summary.

- Synopsis

  The synopsis was updated to align with body text in the document.

- Section 2.4.2.3 Efficacy

  The above section was updated to include information on patients with *BRAF*-mutant melanoma who had been rechallenged with combination BRAF/MEK inhibitor therapy following prior BRAF inhibitor therapy.

- Section 4.1 Study Design Overview

  The above section was clarified to state that patients in the post-DDI phase will be followed per local standard-of-care practice and to specify that, in the post-DDI phase, <u>all</u> SAEs should be reported to the Sponsor.

- Section 4.12 Post-DDI Phase; Section 8.5.1 [Post-DDI Phase] To Occur Every 3-4 Weeks; Section 8.5.2 [Post-DDI Phase] Day 30 Safety Follow-up Visit; Section 8.5.2 Table 8 Schedule of Events

  The above sections were clarified to specify that, in the post-DDI phase, <u>all</u> SAEs should be reported to the Sponsor.

- Section 5.2.1 Inclusion Criteria

  The above section was modified as follows:

  - Inclusion Criterion 6: Patients with unresectable locally advanced or metastatic melanoma permitted to have prior BRAF and/or MEK inhibitor therapy, provided it was not in the regimen immediately prior to study entry.
  - Inclusion Criterion 7: Patients with other (non-melanoma) *BRAF* V600-mutant advanced solid tumors permitted to have prior BRAF and/or MEK inhibitor therapy, provided it was not in the regimen immediately prior to study entry, and specifies that enrollment of patients who progressed on such prior therapy must be discussed with the Sponsor.

- Inclusion Criterion 10: Reformatted to present items using letters, rather than bullets, for consistency with other eligibility criteria.

- Section 5.2.2 Exclusion Criteria

  The above section was modified as follows:

  - Exclusion Criterion 12: Prior BRAF/MEK inhibitor therapy was removed as an exclusion criterion; discontinuation of such therapy for toxicity was added as an exclusion criterion.

- Section 10.1 Adverse Event; Section 10.2 Adverse Events Related to Progression of Disease; 10.4 Clinical Laboratory Abnormalities; Section 10.6 Assessment of Severity; Section 10.7 Assessment of Causality; Section 10.8 Assessment of Seriousness; Section 10.9 Reporting of Serious and Nonserious Adverse Events; Section 10.10 Reporting of Suspected Unexpected Serious Adverse Events; Section 10.11 Pregnancy or Drug Exposure During Pregnancy; 10.12 Review of Safety Data

  The above sections were updated with current Sponsor language regarding documentation of adverse events.

- Section 10.3 Adverse Events Related to Subsequent Anti-Cancer Therapy

  The above section was deleted.

- Section 15 References

  The above section was updated to include a new reference.

- Appendix 7 Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1

  The above appendix was updated to correct numbering of section headings.

IRB/IEC/HA

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Amendment 2

Amendment Rationale

The reason for the current amendment is to clarify certain study procedures (e.g. assessment of coagulation; urine PK is for Arm 1 only), add more detailed guidance on contraception and ultraviolet light exposure and ensure consistency of wording among protocol sections. In addition, minor changes for consistency and clarification were implemented.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol. All changes made in the body of the protocol are reflected in the Protocol Summary.

- Synopsis
  The synopsis was updated to clarify that the order of the CYP probe cocktail ingredients as listed is the order in which they should be taken.

  The synopsis was also updated for eligibility criteria to clarify content and align with body document text.

  The synopsis was also updated to clarify when patient replacement is required.
- Section 2.5.1 Rationale for the Study
  The above section was updated to add the impact of encorafenib on metabolic processes.
- Section 3.2 Study Endpoints
  The above section was minimally revised to align wording between synopsis and body of document.
- Section 4.1.1 DDI Phase
  The above section was updated to clarify that urine PK assessment is for patients in Arm 1 only and to clarify when patient replacement is required.
- Section 4.2.1 Encorafenib and Binimetinib
  The above section was updated to correctly state the formulation of encorafenib as a capsule rather than a tablet. In addition, Added that encorafenib and binimetinib can be taken with or without food on non-PK days. Added that the order of the CYP probe cocktail ingredients is the order in which they should be taken.
- Section 4.3 Duration of Treatment
  The above section was updated to updated to clarify the timing of Prescreening and Screening.
- Section 5.2.1 Inclusion Criteria
  The above section was updated to separate Inclusion Criterion #6 into 2 separate criteria (added new Inclusion Criterion #7) to clarify the prior therapy criteria for patients with unresectable locally advanced or metastatic melanoma (e.g., naïve, untreated patients or patients who have progressed on or after prior systemic therapy) and for patients with other (non-melanoma) *BRAF* V600-mutant advanced solid tumors (e.g., who have progressed on standard therapy or for whom there are no available standard therapy).

- Section 5.2.2 Exclusion Criteria
  The above section was updated for Exclusion Criteria #3 and 4 to clarify content and align with body document text pertaining to concomitant medications. Exclusion criterion #6 was revised to reflect current eligibility criteria for encorafenib and binimetinib protocols for retinal vein occlusion (RVO). Exclusion criterion #7b was corrected for left ventricular ejection fraction (LVEF) to be < 50%. Corrected wording of Exclusion Criterion 9 and replace "encorafenib" with "study drugs" to match wording in synopsis.
- Section 5.3.1 Requirements for Contraception
  In the above section, clarified that use of contraception is required for all males and females of childbearing potential from Screening through 90 days and 30 days, respectively, after the last dose of study drug.
- Section 5.3.2 Ultraviolet Light Exposure
  The above section was added to recommend use of precautionary measures against ultraviolet exposure.
- Section 5.4.2.1 Prohibited Concomitant Medications
  The above section was updated to to clarify content and align with exclusion criteria pertaining to concomitant medications.
- Section 6.1 Dosing Regimen
  The above section was updated to clarify that the order of the CYP probe cocktail ingredients is the order in which they should be taken.
- Section 6.4 Study Drug Dispensing and Administration
  Section was revised to clarify that dosing diaries will be provided at each study visit.
- Section 6.5 Dose Modifications and Reductions, Table 4 Dose Reduction for Encorafenib
  The above section was updated to clarify when patient replacement is required due to dose modifications. The dose reduction table for encorafenib was revised to list the lowest dose option to be used with encorafenib.
- Section 7.1.6 Clinical Laboratory Tests and Table 7 Summary of Clinical Laboratory Tests
  Drug and alcohol testing on Day -7 at Hour 0 was added to the table to match the study procedures.
- Section 7.2 Pharmacokinetic Assessments
  The above section was updated to correct that timepoints indicated are 0 hour through 8 hours, rather than 1 hour through 8 hours, and to add that patient should void as close to the 8 hour time point as possible. The text was clarified to state that the urine PK assessments are for Arm 1 only.
- Sections 8.2 Screening Evaluations, 8.3.1.1 (Day -7 at Hour 0), 8.3.1.4 (Day 1 and Day 14 at Hour 0) and 8.4 (Day 28, End of DDI Phase Visit)
  The above sections were updated to add that coagulation will also be assessed from the blood sample collected and Day -7 urinalysis will include drug and alcohol testing.

- Sections 8.3.1.1 (Day -7 at Hour 0), 8.3.1.2 (Day -7 at Hours 1 and 3), 8.3.1.3 (Day -7 at Hours 2, 4, 6 and 8), 8.3.1.4 (Day 1 and Day 14 at Hour 0), 8.3.1.5 (Day 1 and 14 at Hours 1 and 3) and 8.3.1.6 (Day 1 and Day 14 at Hours 2, 4, 6 and 8)
  The above sections were updated to clarify that urine PK collection is for Arm 1 only.

- Table 8 Schedule of Events
  The above table was updated to add coagulation assessments, clarify that urine PK assessment is for patients in Arm 1 only and to correct footnote numbering. Added to footnote "L" that drug and alcohol screen are part of the Day -7 urinalysis.

- Section 9.1 Treatment Discontinuation of Individual Patients
  The above section was updated to clarify that a patient will be discontinued from treatment if he/she misses encorafenib or binimetinib dosing for > 28 days in the post-DDI phase.

  The above section was updated to clarify that an AE dose delay in requiring treatment discontinuation includes delay in the post-DDI phase of more than 28 days to restart treatment due to an AE.

- Section 9.2 Replacement of Patients
  The above section was updated to clarify when patient replacement is required.

- Section 11.1.1 Sample Size
  The above section was updated to align with wording in synopsis (analysis based on mean AUC_{last}).

- Section 11.1.3 Pharmacokinetic Analysis
  The above section was updated to clarify that patients who have sufficient concentration data to calculate at least one PK parameter on Day -7, Day 1 and Day 14 will be included in the PK analyses and to correct day range used in analyses.

- All Appendices
  Appendices headers were corrected for the study number.

- Appendix 9: ECOG performance status
  The above appendix table was added for ease of use.

IRB/IEC/HA

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Amendment 1

Amendment Rationale

The reason for the current amendment is to clarify certain study procedures (e.g. follow-up in the DDI phase), add as an inclusion criterion that patients must be non-smokers, add as an exclusion criterion consumption of specific products containing citrus juice and add additional laboratory parameters for assessment.
In addition, minor changes for consistency and clarification were implemented.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. All changes made in the body of the protocol are reflected in the Protocol Summary.

- Section 2.2.2.1 Clinical Pharmacology
  The above section was updated to include study numbers and add the encorafenib T_{max} data.
- Section 2.2.2.2.1 Encorafenib Monotherapy in Patients with Advanced Cancer
  The above section was updated to include data on determination of the encorafenib single-agent dose of 300 mg QD.
- Section 2.3.2.1 Clinical Pharmacology
  The above section was updated to include study numbers and add the binimetinib T_{max} data.
- Section 2.3.2.2.1 Binimetinib Monotherapy in Patients with Advanced Cancer
  In the above section, data from binimetinib studies with combination agents other encorafenib were deleted due to lack of relevance to this protocol.
- Section 2.4.2.2 Safety
  The above section was updated clarify the studies providing safety data. Information on AE withdrawal and deaths was deleted and directed to the Investigator's Brochure for further information.
- Section 4.1 Study Design Overview; Section 4.1.2 Post-DDI Phase; Section 8.5.1 To Occur Every 3-4 Weeks; Section 8.5.2 Day 30 Follow-up Visit; Table 9; Section 10.9 Reporting of Serious and Nonserious Adverse Events
  The above sections were updated clarify the safety follow-up and data collection in the post-DDI phase.
- Section 4.2.1 Encorafenib and Binimetinib
  The above section was updated to clarify that binimetinib and encorafenib are to be taken together and to add clarification on consumption of products containing citrus juice.
- Section 5.2.1 Inclusion Criteria
  The above section was updated to only include non-smoking patients who had not used products with nicotine within 3 months of first dose of study drugs.
- Section 5.2.2 Exclusion Criteria
  The above section was updated to exclude consumption of specific products containing citrus juice and to exclude patients with a positive cotinine test.

- Section 5.3.1 Requirements for Contraception
  The above section was updated to clarify that oral, injectable, or implanted contraceptives were acceptable only when combined with other highly effective or acceptable methods.
- Section 5.4.2.1 Prohibited Concomitant Medications
  The above section was updated to prohibit consumption of specific products containing citrus juice.
- Section 6.5 Dose Modifications and Reductions
  The above section was updated to clarify that if encorafenib was to be continued as monotherapy, it be at 300 mg QD.
- Section 6.5.1 Follow-up for Toxicities
  The above section was updated to clarify that all doses and dose changes are to be captured on the eCRF.
- Section 7.1.6 Clinical Laboratory Tests – Table 8
  The above section was updated to add assessment of amylase, LDH, lipase, aPTT, PT or INR.
- Table 9 – Schedule of Events
  The above section was updated to add that BOR was to be assessed at the Day 30 Follow-up Visit.

IRB/IEC/HA

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1. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Investigator is the person responsible for the conduct of the study at the investigational site. A subinvestigator is any member of the clinical study team designated and supervised by the Investigator to perform critical study-related procedures and/or to make important study-related decisions.

Prior to study initiation, the Principal Investigator at each site must provide to Array BioPharma Inc. (a wholly owned subsidiary of Pfizer Inc./Sponsor) a signed protocol signature page, a fully executed and signed United States (US) Food and Drug Administration (FDA) Form 1572, a current curriculum vitae (CV), medical license and a financial disclosure form. Financial disclosure forms, current CVs and medical licenses must also be provided for all subinvestigators listed on Form 1572 who will be directly involved in the treatment or evaluation of patients in this study.

The study will be administered and monitored by employees or representatives of the Sponsor and/or a contract research organization (CRO) in accordance with all applicable regulations. Clinical research associates (CRAs) will monitor each site on a periodic basis and perform verification of source documentation for each patient. Pfizer Safety (and/or the CRO, if applicable) will be responsible for ensuring timely reporting of expedited serious adverse event (SAE) reports to regulatory authorities and Investigators.

2. INTRODUCTION

2.1. BRAF Mutation-Positive Cancer

Activating mutations in the gene encoding the serine – threonine protein kinase BRAF were identified in large-scale screens in human cancers (Davies et al 2002). After this first report of BRAF mutations was described in 2002, several other BRAF mutation studies in different tumors types were reported. It is now well established that 90% of reported *BRAF* mutations result in a substitution of valine by glutamic acid at amino acid 600 (V600E mutation) which leads to a 500-fold increase in BRAF activity compared to wild-type BRAF (Wan et al 2004). More than half of patients with metastatic melanoma have mutations in *BRAF*, and over 95% of these are in BRAF exon 15 at V600 (Davies et al 2002). Somatic mutations of BRAF also occur in 8-15% of colorectal cancers, (Rajagopalan et al 2002; Hodis et al 2012; Krauthammer et al 2012), in 30% of serous borderline ovarian cancers (Singer et al 2003), in 40-70% of papillary thyroid carcinomas (Brose et al 2002; Cohen et al 2003; Nikiforova et al 2003; Fukushima et al 2003) and in 7-8% of all solid tumors (Brower 2010), implicating activating oncogenic mutations of *BRAF* as critical promoters of malignancy.

The most common V600 mutations in metastatic melanoma are V600E and V600K accounting for 66-91% and 7-30% of all *BRAF* V600 mutations, respectively (Cheng et al 2011; Colombino et al 2012; Jakob et al 2012; Greaves et al 2013). These mutations constitutively activate BRAF protein and downstream signal transduction in the RAF/MEK/ERK pathway, which signals for cancer cell proliferation and survival.

Melanoma is a cancer that primarily arises from melanocytes, the cells that produce the pigment melanin. Both the incidence and mortality rate of melanoma are rapidly increasing throughout the world, constituting a significant and growing health burden (Ferlay et al 2015; American Cancer Society 2016). The worldwide incidence of melanoma in 2012 was estimated at over 232,000 (data source GLOBOCAN 2016 at Cancer Today; http//gco.iarc.fr/today/home), and it is estimated that over 76,000 people will be diagnosed and that over 12,000 deaths will be attributed to melanoma in 2016 in the US alone (Siegel et al 2016; American Cancer Society 2016).

Although the current MEK/BRAF inhibitor combinations have transformed the standard-of-care treatment for melanoma, they each have liabilities that could limit their effectiveness suggesting that additional therapeutic options are needed. Advanced *BRAF* V600-mutated melanoma remains an aggressive disease that portends a poor prognosis and there remains a need to develop new treatment regimens to expand the therapeutic options for patients. Encorafenib (LGX818) and binimetinib (also known as MEK162 or ARRY-438162) are being developed to inhibit the growth of tumors with activating mutations of the RAS/RAF/MEK/ERK pathway.

2.2. Drug-Drug Interaction Potential

Metabolic routes of elimination, including those occurring through the cytochrome P450 (CYP) family of enzymes and uridine diphosphate (UDP)-glucuronosyl transferases (UGTs), and uptake and efflux transporters can be inhibited and/or induced by concomitant drug treatment. Changes arising from these drug-drug interactions can be significant, and contribute to increases or decreases in the blood and tissue concentrations of the parent drug

or active metabolite. Increased concentrations of a parent drug or its active metabolite can alter the safety and efficacy profile of a drug. It is, therefore, important to determine if metabolic drug-drug interactions are likely to significantly affect the elimination of a drug.

The FDA guidance for Drug Interaction studies recommends evaluating the extent of enzyme and transporter inhibition and/or induction by conducting a study with probes sensitive to changes in activity of the corresponding enzyme or transporter (Food and Drug Administration. Guidance for Industry 2012). The main purpose of this study is thus to evaluate the potential effect of encorafenib in combination with binimetinib on enzymes and transporters of interest *in vivo* (see Section 2.6.1).

2.3. Overview of Encorafenib

Encorafenib is a novel oral small-molecule kinase inhibitor with potent and selective inhibitory activity against mutant BRAF kinase, a member of the murine leukemia viral oncogene homolog (RAF)/ mitogen-activated protein (MAP) kinase kinase (MEK)/ extracellular regulated signal kinase (ERK)/ MAP kinase (MAPK) pathway, which plays a prominent role in controlling several key cellular functions including growth, proliferation, and survival.

Encorafenib is currently being investigated as a single-agent and in combination with other agents including inhibitors of the MEK, phosphoinositide 3-kinase (PI3K), epidermal growth factor receptor (EGFR), cyclin-dependent kinase 4/6 (CDK4/6), porcupine homolog (PORCN) and cMET proteins in patients with selected advanced or metastatic *BRAF*-mutated solid tumors, such as melanoma, colorectal, lung and thyroid cancers.

2.3.1. Nonclinical Studies with Encorafenib

2.3.1.1. Nonclinical Pharmacology

2.3.1.1.1. Target Inhibition

Encorafenib is a highly selective adenosine triphosphate (ATP) competitive small-molecule RAF kinase inhibitor which suppresses the RAF/MEK/ERK pathway in tumor cells expressing *BRAF*V600E. For example, the half maximal response concentration (EC_{50}) for suppression of phosphorylated MEK (pMEK) and phosphorylated ERK (pERK) in A375 human melanoma cells are 2 nM and 3 nM, respectively. Suppression of the RAF/MEK/ERK pathway causes cell cycle arrest which leads to inhibition of cell proliferation with an EC_{50} = 4 nM. Similar to other selective small molecule RAF kinase inhibitors, encorafenib inhibits CRAF, BRAF, as well as BRAFV600E in cell-free assays; however, this class of inhibitor does not inhibit RAF/MEK/ERK signaling in cells expressing wild-type BRAF. Given both the high degree of selectivity of encorafenib for the RAF kinases in biochemical assays (only 2/75 non-RAF kinases inhibited at concentrations < 1 μM), and the failure of encorafenib to inhibit wild type RAF kinases in cells, encorafenib has no antiproliferative activity in tumor cell lines that express wild-type BRAF.

The metabolite NVP-LYH746 (also known as M42.5A) was assessed for its off-target activity on 56 G protein coupled receptors, transporters, ion channels, nuclear receptors and enzymes since this metabolite represented 15.5% of total radioactivity in plasma in the

human absorption, distribution, metabolism, and excretion (ADME) study. The results showed activities of > 50% inhibition at 10 μM were found on kinase insert domain receptor (half maximal inhibitory concentration [IC_{50}] = 1.8 μM, n = 1) and phosphodiesterase 4D (PDE4D) (IC_{50} = 4.2 μM, n = 2), showing significantly less potency than encorafenib.

The narrow kinase profile and potent antiproliferative activity of encorafenib translates into a very wide therapeutic index in vivo. In mouse and rat xenograft models of human melanoma expressing BRAFV600E, encorafenib induces tumor regression at doses as low as 5 mg/kg and 1 mg/kg, respectively (~360 ng*hr/mL free drug plasma exposure). Tumor regression was associated with continuous and strong (> 75%) suppression of pMEK, pERK, and downstream transcriptional targets dual specificity phosphatase 6 (DUSP6) and SPRY4. By contrast, encorafenib was tolerated in the 1 month Good Laboratory Practice (GLP) toxicology study at doses up to 100 mg/kg in males and females (5140 ng*hr/mL in cyno and 23400 ng*hr/mL in rats free drug exposure). Taken together, these data suggest that encorafenib has a wide therapeutic index (> 11 fold) and that regression of *BRAF*V600E human melanoma tumor xenografts is associated with a strong and sustained inhibition of the RAF/MEK/ERK pathway.

2.3.1.1.2. Nonclinical Absorption, Distribution, Metabolism, Excretion and Pharmacokinetics

The oral bioavailability (F) of encorafenib was ~40 to ~50% in the mouse, rat, and dog. In the monkey ADME study, F was low (22%). Encorafenib showed low plasma clearance in the rat and mouse and a moderate to high plasma clearance in the monkey and dog. The estimated volume of distribution at steady state (Vss) was low in the rodents and moderate in the dog and monkey. In the monkey 13-week toxicity study, encorafenib increased proportionally with dose and no accumulation upon multiple dosing.

Encorafenib is a substrate of P glycoprotein (P-gp) with a high apparent passive permeability. Binding to human plasma proteins was ~86%.

Distribution into rat tissues was rapid. There was no distribution to the central nervous system (CNS; brain and spinal cord) and no retention in the melanin-rich tissues.

For all species investigated, monohydroxylation, N-dealkylation, and subsequent glucuronidation represented the major metabolic pathways. Glucuronidation, both direct and indirect, occurred more readily in human than in other species. Encorafenib is metabolized by cytochrome P450 (CYP) 3A4, CYP2C19, and CYP2D6. CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%), followed by CYP2C19 and CYP2D6 (~16.0% and 0.71%, respectively).

The predominant route of excretion of ^{14}C-encorafenib in monkeys was via fecal excretion while the urinary excretion was a minor route of elimination. Encorafenib is predominantly excreted as metabolites.

In vitro experiments indicate that encorafenib is a relatively potent reversible inhibitor of uridine 5'-diphospho (UDP)-glucuronosyltransferase-glucuronosyltransferase 1A1

(UGT1A1), CYP2B6, CYP2C9, and CYP3A4/5, and also a time-dependent inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9, and CYP3A4 in human primary hepatocytes. Finally, encorafenib was found to be a weak inhibitor of breast cancer resistance protein (BCRP), and a potent inhibitor of renal transporters organic cation transporter (OCT) 2, organic anion transporter (OAT) 1, OAT3 and hepatic transporters OCT1, organic anion transporting polypeptide (OATP) 1B1 and OATP1B3.

2.3.1.2. Nonclinical Toxicity and Safety

Preclinical safety pharmacology data do not indicate a clinical risk for QTc prolongation, or adverse effects on the CNS or respiratory system. Administration of encorafenib to male albino rats as a single oral dose of 100 mg/kg produced no drug related effects on the CNS or respiratory system. In Good Laboratory Practice (GLP) 4- and 13 week oral (gavage) toxicity studies in monkeys and a GLP monkey telemetry study, encorafenib had no effect on electrocardiographic morphology, rhythm, or PR, QRS, QT, and QTc duration. Using cloned human ether-à-go-go related gene (hERG) potassium channels expressed in mammalian cells, the IC_{50} for hERG inhibition by encorafenib was determined to be 73.4 μM indicating an unlikely effect of encorafenib on QTc prolongation. Encorafenib was evaluated for safety in rats and cynomolgus monkeys in studies for up to 13 weeks in duration. Overall, encorafenib was well tolerated. There were findings believed to be associated with the pharmacologic activity of a BRAF kinase inhibitor activation of the RAF/MEK/ERK pathway. These included hyperplasia and hyperkeratosis in the skin (plantar surface of feet) and nonglandular stomach in rats. Additional toxicity was observed in the 4- and 13-week GLP rat study in the testes/seminiferous tubules and epididymides that included an absence of the later stages of spermatid maturation. This finding did not appear to be reversible in affected tubules in the 4-week rat study, but the 13-week rat study showed evidence of recovery. There was significant mortality/morbidity in rats (mostly females) at the highest dose (400 mg/kg/day) in the 4-week rat study. In these early death rats, significant lesions were seen in the kidneys, liver, stomach, esophagus, bone marrow, spleen, thymus, lymph nodes, pancreas, adrenal glands, and parathyroid glands. However in the 4 female rats that survived the recovery, there were no histopathologic findings indicating these toxicities were reversible.

The formulation used in the 4-week GLP monkey study, 56:29:15% (w:w:w) PEG400:Cremophor EL:oleic acid, has given the best exposure but causes significant diarrhea in all groups, including the vehicle control animals. The high dose (100 mg/kg/day) was associated with increased severity of diarrhea and slight body weight loss.

In the 13-week monkey study with a solid dispersion formulation, at doses up to 60 mg/kg/day, the only test article-related finding was abnormal retina (with blister like lesions over the macular region) in 2 high-dose animals. This finding showed evidence of recovery in one of the affected animals. Histopathology examination of the affected eyes suggested that the findings were similar to retinopathy associated with MEK inhibitor.

The GLP Ames and chromosomal aberration assays as well as a rat micronucleus study indicate that encorafenib is not genotoxic. Encorafenib showed a potential for phototoxicity in a screen 3T3 NRU in vitro assay. Additionally, encorafenib did not show a sensitizing

potential in the murine LLNA TIER I assay, although revealed a weak irritating potential. However, it tested negative in the primary skin irritation assay in rabbits.

Embryo-fetal development studies show evidence of delayed skeletal development secondary to decreased fetal body weight at maternally toxic doses in rabbits and in rats decreased ossification that is considered to be secondary to decreased fetal body weight as a result of moderately decreased maternal body weights.

Detailed information regarding nonclinical studies of encorafenib is presented in the Investigator's Brochure.

2.3.2. Clinical Experience with Encorafenib

2.3.2.1. Clinical Pharmacology

The human ADME study in healthy subjects (CLGX818A2101) showed that encorafenib is at least 86% absorbed based on recovered radioactivity and has a preferential distribution to plasma as compared to blood. The predominant biotransformation reaction of encorafenib was N-dealkylation (other major metabolic pathways involved hydroxylation, carbamate hydrolysis, indirect glucuronidation and glucose conjugate formation.). The most abundant circulating component was encorafenib, ranging from 17.9% to 36.4% of the radioactivity in plasma. Encorafenib was mainly eliminated via metabolism, with low levels of unchanged encorafenib detected in urine and feces. The dose was equally recovered in urine and feces (47.2% in each matrix) and the renal clearance was estimated to be 1.8%. The terminal elimination half-life of encorafenib as observed in patients is approximately 3.5 hours (Study CMEK162X2110).

Preliminary results from a food-effect clinical study (ARRAY-818-102) have indicated that the influence of food on the PK of encorafenib is mild and not clinically relevant; therefore, encorafenib can be taken without regard to food. Preliminary results from Study ARRAY-162-105, an ongoing drug interaction study in healthy subjects, indicate that the extent of encorafenib exposure is not altered in the presence of the proton-pump inhibitor rabeprazole.

Encorafenib as a single-agent in patients with locally advanced or metastatic *BRAF*-mutant melanoma in the dose-escalation phase of Study CLGX818X2101 showed that the Day 15 exposures were consistently decreased by 30 to 60% compared to those at Day 1, probably due to induction of CYP enzymes. Area under the plasma concentration time curve (AUC) and maximum observed plasma concentration (C_{max}) ratios at steady state (Day 15) relative to Day 1 did not appear to change with dose. The dose-expansion phase in patients with locally advanced or metastatic BRAF-mutant melanoma or metastatic colorectal cancer (mCRC) showed exposure of encorafenib in terms of C_{max} and AUC over the final dosing interval (tau) (AUC_{tau}) was within the range observed at the 300-mg dose level for the dose-escalation phase. Encorafenib T_{max} was consistent across dose levels and days at 2 hours.

The results of the dose-proportionality assessment in patients with locally advanced or metastatic *BRAF*-mutant melanoma suggest that encorafenib exposure was approximately dose proportional over the dose range studied.

In combination studies, when administered with binimetinib, pharmacokinetic (PK) parameters of encorafenib were similar to those observed in the single-agent study.

2.3.2.2. Clinical Safety

As of the data cutoff date of 11 May 2016, a total of 1495 healthy subjects and patients with advanced cancer had received at least one dose of encorafenib, either as a single agent, in combination with targeted agents, or in the case of one patient, both monotherapy and combination therapy, in 13 completed or ongoing human studies in which safety parameters either were or are currently being assessed. These patients constitute the encorafenib safety population, which includes 91 healthy subjects and 1404 patients with advanced cancer. Based on the experience from these ongoing studies, encorafenib has demonstrated an acceptable and manageable safety profile.

2.3.2.2.1. Encorafenib Monotherapy in Patients with Advanced Cancer

As of the data cutoff date of 11 May 2016, 414 patients with advanced cancer have received at least one dose of encorafenib monotherapy in 4 clinical studies. The safety and tolerability of encorafenib was first evaluated in Study CLGX818X2101, a Phase 1 open-label, multi-center, dose-escalation and expansion study in adult patients with BRAF V600-mutant locally advanced or metastatic melanoma or metastatic colorectal cancer (mCRC) (expansion part only). Doses up to 700 mg QD were assessed in the dose escalation portion of the study and the maximum tolerated dose (MTD) was determined to be 450 mg QD. Of the 34 patients enrolled at the MTD in the dose expansion, 9 patients were considered to have a dose-limiting toxicity (DLT) during the first cycle. Eighteen (52.9%) patients at the MTD required at least 1 dose reduction. As a result of the DLTs and number of patients requiring dose reductions, the 300-mg dose level was declared as the recommended Phase 2 dose (RP2D).

Across the monotherapy studies, the most common adverse events (AEs) (≥ 20% of patients), regardless of grade and dose, were dermatological (palmar-plantar erythrodysaesthesia syndrome [PPES], hyperkeratosis, keratosis pilaris, pruritus, alopecia, dry skin, erythema, melanocytic naevus, xerosis, rash), gastrointestinal (nausea, vomiting, decreased appetite), musculoskeletal (arthralgia, myalgia, pain in extremity), fatigue, asthenia, insomnia and headache.

Refer to the Investigator's Brochure for more detailed information on encorafenib.

2.4. Overview of Binimetinib

Binimetinib is an orally bioavailable, selective and potent MEK 1 and MEK 2 inhibitor.

As a MEK inhibitor, this compound has the potential to benefit patients with advanced cancers by inhibiting the RAS/RAF/MEK/ ERK pathway. Binimetinib has previously been examined in the treatment of rheumatoid arthritis based on the role of the RAS/RAF/MEK/ERK pathway in inflammatory processes.

Binimetinib is currently being investigated as a single agent and in combination with a variety of additional compounds, including paclitaxel and inhibitors of PI3K, RAF, EGFR, protein kinase C (PKC), CDK4/6 and type 1 insulin-like growth factor receptor (IGF-1R) in

patients with selected advanced or metastatic solid tumors, including, among other tumors, melanoma, biliary, colorectal and ovarian cancers. The clinical development program of binimetinib encompasses patients with selected advanced or metastatic solid tumors, including neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*)- and *BRAF*-mutant melanoma, BRAF- and Kirsten rat sarcoma viral oncogene homolog (KRAS)-mutant non-small cell lung cancer (NSCLC), high-grade platinum-resistant ovarian cancer, low-grade serous ovarian cancer, biliary, colorectal and pancreatic cancers.

2.4.1. Nonclinical Studies with Binimetinib

2.4.1.1. Nonclinical Pharmacology

2.4.1.1.1. Target Inhibition

Binimetinib is an ATP-uncompetitive inhibitor of MEK1/2. In cell-free systems, binimetinib inhibits MEK1/2 with a IC_{50} of 12 nM. In vitro, binimetinib potently inhibits MEK-dependent phosphorylation of ERK in human BRAF-mutant melanoma cell lines, including A375, IGR-1, IGR-39, Colo-800, MDA-MB-435S, RPMI-7951, UACC-62, and WM-115, as well as NRAS-mutant melanoma lines, such as IPC-298, Hs944.T, MEL-JUSO, SK-MEL-2 and SK-MEL-30. In vivo, binimetinib treatment results in dose- and time-dependent inhibition of phosphorylation of ERK in the HT-29 human colorectal cancer (CRC) xenograft. Similarly, levels of both pERK and DUSP6 messenger ribonucleic acid (mRNA) (a target gene of pERK) are reduced in the A375 melanoma xenograft. Lastly, in ex vivo experiments, binimetinib reduces pERK levels in human whole blood cells.

2.4.1.1.2. Nonclinical Absorption, Distribution, Metabolism, Excretion and Pharmacokinetics

The F in rat and monkey ADME studies was moderate (48%) and similar to the fraction absorbed (based on radioactivity excreted), suggesting a minimal first pass effect. Binimetinib showed a low total systemic plasma clearance and volume of distribution at steady state after intravenous (IV) administration, and mean plasma terminal half-life ($t_{1/2}$) has ranged from 2 to 9 hours in preclinical species.

In vitro experiments indicate that binimetinib has moderate to high membrane permeability and is a substrate of P-gp and BCRP.

Binimetinib is highly bound to plasma proteins (humans: 97.2%).

Binimetinib is more distributed in plasma than blood. The blood-to-plasma concentration ratios of binimetinib have ranged from 0.652 to 0.994 in the species tested. In humans, the blood-to-plasma ratio was 0.718.

^{14C}-binimetinib-derived radioactivity was absorbed and widely distributed to tissues in both pigmented rats and albino rats following a single oral (PO) dose.

With multiple routes of metabolism, binimetinib was metabolized primarily by glucuronidation pathways (mainly via UGT1A1, 1A3 and 1A9) and to a lesser extent by oxidation pathways (mainly via CYP1A2 and CYP2C19). UGT1A1 was shown to be the major contributor (90%) to the formation of the direct glucuronide.

Following IV dosing in the rat, fecal and urinary excretion accounted for 46% and 45% of total radioactivity, respectively. Approximately 15% and 16% of binimetinib was excreted unchanged in urine and feces, respectively. The total recovery of radioactivity in the excreta of monkeys was 99% and 85% following PO and IV dosing, respectively. The most abundant drug-related components in monkey excreta included binimetinib, the 2 glucuronides and the amide.

In vitro, binimetinib reversibly inhibits CYP2B6 and is a weak reversible inhibitor of CYP1A2 and CYP2C9. Binimetinib is not considered a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5. Binimetinib has also induced CYP3A, but this induction was not confirmed in a human drug-drug interaction (DDI) study.

2.4.1.2. Nonclinical Toxicity and Safety

Binimetinib and its active metabolite, AR00426032, showed no significant hERG channel inhibition (IC_{50} of each > 30μM). In telemeterized monkeys, no effects were observed on electrocardiogram (ECG) wave-forms or cardiac intervals including QTc at doses as high at 10 mg/kg where exposure exceeded that attained clinically at the MTD of 60 mg twice daily (BID).

Repeat-dose toxicological studies indicated that binimetinib was tolerated at doses up to 30 mg/kg for 28 days or 10 mg/kg for 6 months in rats and up to 3 mg/kg for 28 days or 2 mg/kg for 9 months in monkeys. The most prominent in vivo findings were dose-related, reversible hair loss and/or scabbing in rats and loose or watery stools in monkeys.

Administration of binimetinib to rats was associated with microscopic findings of soft tissue mineralization, skin effects and minimal to mild clinical pathology changes. Gastric mucosal lesions were associated with single-dose binimetinib administration to rats at 100 mg/kg. In cynomolgus monkeys, administration of binimetinib was associated with soft stools, moderate clinical pathology changes in some animals and reversible histopathologic changes in the gastrointestinal tract.

No evidence of genotoxicity was observed from the 2 in vitro assays (bacterial reverse mutation or mouse lymphoma) or the in vivo assay (mouse erythrocyte micronucleus).

Embryo-fetal development studies showed evidence of teratogenicity in rabbits (ventricular septal defects and outflow tract defects) and in rats decreased ossification that was considered to be secondary to decreased fetal body weight at maternally toxic doses.

Daily oral administration of binimetinib to juvenile Sprague-Dawley rats on postnatal Day 10 through 40 was not tolerated at doses ≥ 10 mg/kg/day. The MTD in juvenile rats was 3 mg/kg and the no-observable-adverse-effect level (NOAEL) was 1 mg/kg/day.

Detailed information regarding nonclinical studies of binimetinib is presented in the Investigator's Brochure.

2.4.2. Clinical Experience with Binimetinib

2.4.2.1. Clinical Pharmacology

The PK of binimetinib are characterized by moderate to high variability, accumulation of approximately 1.5-fold, and steady state concentrations reached within 15 days. Binimetinib T_{max} tends to range from 1.5 to 2 hours. Binimetinib has been shown to be approximately dose proportional (Study ARRAY-162-111). The human ADME study (CMEK162A2102) indicated that approximately 50% of binimetinib dose was absorbed. The primary metabolic pathways include glucuronidation (up to 61.2% via UGT1A1), N-dealkylation, amide hydrolysis (up to 17.8% via CYP1A1 and CYP2C19). The excretion route was 31.7% of unchanged binimetinib in feces and 18.4% in urine. Estimated renal clearance of unchanged binimetinib was 6.3% of total dose. The impact of UGT1A1 inhibitors or inducers has not been clinically assessed.

Food-effect clinical studies have indicated that the influence of food on the PK of binimetinib is mild and not clinically relevant; therefore, binimetinib can be taken with food (ARRAY-162-104 and CMEK162A2103). Results from a drug interaction study with binimetinib and midazolam suggested that continuous intake of binimetinib produced no relevant CYP3A4 induction (CMEK162A2105). Binimetinib solubility in vitro has been shown to be pH dependent. Preliminary results from an ongoing drug interaction study in healthy subjects indicate that the extent of binimetinib exposure is not altered in the presence of the proton-pump inhibitor rabeprazole (ARRAY-162-105). In vitro studies also demonstrated that binimetinib is a P-gp and BCRP substrate, but the effects of inhibitors of these substrates on the PK of binimetinib in vivo are unknown.

Preliminary results from an ongoing hepatic impairment study (CMEK162A2104) indicate that the exposure of binimetinib in healthy subjects and those with mild hepatic impairment is comparable, while a potential increase in exposure is observed in subjects with moderately impaired hepatic function. Exposure in subjects with severe hepatic impairment has not yet been determined.

2.4.2.2. Clinical Safety

As of 20 January 2016, a total of 2555 healthy subjects and patients had received at least one dose of binimetinib and are therefore eligible for inclusion in the overall safety population of binimetinib, which comprises 220 healthy subjects, 164 patients with rheumatoid arthritis, 12 patients with hepatic dysfunction and 2159 patients with advanced cancer.

2.4.2.2.1. Binimetinib Monotherapy in Patients with Advanced Cancer

Binimetinib has been administered as a single agent to 884 patients with cancer across 7 studies.

The recommended single-agent dose of binimetinib is 45 mg BID, which has been evaluated in two Phase 1 studies conducted in patients with advanced solid tumors, advanced or metastatic biliary cancer and *KRAS*- or *BRAF*-mutant mCRC (Study ARRAY-162-111) and in Japanese patients with advanced solid tumors (Study CMEK162X1101); in two Phase 2

studies conducted in BRAFV600 or NRAS-mutant melanoma patients (Study CMEK162X2201) and in advanced solid tumors (Study CMEK162AUS11); in one Phase 2 study conducted in Chinese patients with advanced KRAS/BRAF/NRAS-mutant NSCLC (Study CINC280X2205); and in two Phase 3 studies in patients with NRAS-mutant melanoma (Study CMEK162A2301) and low grade serous carcinomas of the ovary, fallopian tube or primary peritoneum (Study ARRAY-162-311).

Across the monotherapy studies, the most frequently reported AEs considered related to single-agent binimetinib, regardless of grade and binimetinib dose, have been dermatologic events (rash, dermatitis acneiform), gastrointestinal events (nausea, vomiting, diarrhea), edema peripheral, fatigue and increased CK.

Detailed information regarding clinical studies of binimetinib is presented in the Investigator's Brochure.

2.5. Overview of Encorafenib and Binimetinib Combination

2.5.1. Nonclinical Pharmacodynamics

Binimetinib has been combined with several different inhibitors of the MAPK pathway in cell line models derived from a variety of lineages and genetic backgrounds. Combining binimetinib with encorafenib resulted in the overall synergistic inhibition of proliferation in panels of both melanoma- and CRC-derived cancer models. In this case, combination activity was predominantly observed in models with activating mutations in the *BRAF* gene. In vitro, this combination either additively or synergistically inhibited the proliferation of a set of 16 *BRAF* mutant melanoma-derived cell line models. In vivo, this combination significantly increased the conditional survival of mice implanted with a *BRAF*-mutant primary human melanoma xenograft. Although most single agent and all combination treatments effectively inhibited tumor growth, increased survival resulted from reductions in the overall rates (and in some cases complete prevention) of the emergence of resistant tumors in the combination relative to the single agent treatment groups.

2.5.1.1. Nonclinical Pharmacokinetics

2.5.1.1.1. Binimetinib as a Perpetrator on Encorafenib Pharmacokinetics

The biotransformation of encorafenib was mainly through oxidation (see Section 2.3.1.1.2). Encorafenib is metabolized by CYP3A4, CYP2C19 and CYP2D6. The primary CYP responsible for this metabolism is CYP3A4 (approximately 83%).

Encorafenib is relatively potent reversible inhibitor of CYP3A4 and also a time-dependent inhibitor of CYP3A4 (inhibitory constant [K_I] = 20.5 μM and rate of enzyme inactivation [K_{inact}] = 0.0527/min). Furthermore, encorafenib was identified to potentially induce CYP3A4 based on an in vitro PXR reporter gene assay at high concentrations (≥ 10 -50 μM). Exploratory PK in Study CLGX818X2101 (single agent) and Study CMEK162X2110 (combination with binimetinib) showed that Day 15 exposure of encorafenib was consistently lower than that on Day 1 within subjects, indicating auto-induction. Based on in vitro data, binimetinib is not expected to reversibly inhibit CYP3A4, CYP2D6 or CYP2C19. In addition, it did not show time-dependent inhibition of CYP450 enzymes.

2.5.1.1.2. Encorafenib as a Perpetrator on Binimetinib Pharmacokinetics

Nonclinical in vitro data indicate that main pathways of metabolism for binimetinib include glucuronidation by UGT1A1, UGT1A3 and UGT1A9 and to a lesser extent oxidation by CYP1A2 and CYP2C19. UGT1A1 was the primary enzyme to mediate the formation of the direct glucuronide M10.9 (see Section 2.4.1.1.2).

Encorafenib is weak ($IC_{50} \geq 20$ μM) reversible inhibitor of CYP1A2, CYP2C8, CYP2C19 and CYP2D6. Encorafenib is also a UGT1A1 inhibitor with in vitro IC_{50} ranging from 4 to 7 μM. Encorafenib could affect the PK of binimetinib due to inhibition of UGT1A1 but no significant DDI was observed up to the highest dose tested in Study CMEK162X2110.

2.5.1.2. Nonclinical Toxicity and Safety

When combining MEK and RAF kinase inhibitors, the potential for overlapping toxicities needs to be considered. For binimetinib, the predominant toxicities consisted of various skin lesions, including exudates, erosions, inflammation and scabbing and soft tissue mineralization of numerous internal organ (seen in rat) and degeneration of the intestinal epithelium resulting in enteritis (seen in monkeys). For encorafenib, the primary toxicities were skin lesions, including dry, scaly and thickened skin on the plantar surface of the feet, which histologically presented as slight to marked hyperkeratosis, squamous cell hyperplasia and inflammatory cell infiltration, bone marrow hypocellularity, hyperkeratosis and hyperplasia of the non-glandular stomach. Given that MEK and RAF are in the same pathway, it appears likely that gastrointestinal intolerance/toxicity, skin rash and neutropenia may be dose limiting in the clinical setting when these agents are combined. Although retinopathy has not been seen with either compound alone in the preclinical studies, given the retinopathy seen clinically with binimetinib, careful monitoring of ophthalmic effects will be extremely important in the clinical setting.

2.5.2. Clinical Experience with Encorafenib and Binimetinib Combination

2.5.2.1. Clinical Pharmacology

When administered with encorafenib, exposure to binimetinib as described by C_{max} and AUC was within the ranges of values observed in the single-agent studies even though some variability was moderate. There was no trend towards higher or lower C_{max} or AUCs with increasing doses of encorafenib over the entire encorafenib dose range (50 to 800 mg), even though these parameters tended to decrease when increasing the dose of encorafenib to 400 mg. This trend was not observed for encorafenib doses from 450 to 800 mg. The ratio of AUC at steady-state compared with after the first administration was consistent with that observed in single-agent studies, although it seemed to decrease with increasing encorafenib doses. As for AUC, this was attributed to variability. Exposure to the active metabolite AR00426032 was low (~16% or less) compared to that of the parent drug as observed in single-agent studies. The PK parameters of encorafenib co-administered with binimetinib were similar to those observed in the single-agent Study CLGX818X2101.

2.5.2.2. Safety

The primary source of safety data on the combination of encorafenib co-administered with binimetinib is from Study CMEK162B2301. This is a 2-part, ongoing Phase 3, randomized

open-label study of combination encorafenib plus binimetinib treatment versus vemurafenib in patients with locally advanced or metastatic *BRAF*V600 melanoma. Patients have been treated with the combination encorafenib plus binimetinib in 2 additional studies, Study CMEK162X2110 (Phase 1b/2 dose escalation study) and Study CLGX818X2109 (Phase 2 study of the combination encorafenib plus binimetinib followed by addition of targeted agents). Details on Studies CMEK162X2110 and CLGX818X2109 are presented in the Investigator's Brochure.

A total of 192 patients from Part 1 of Study CMEK162B2301 had been treated with the combination of encorafenib plus binimetinib and were evaluable for inclusion in the preliminary safety analyses at the time of data cutoff of 19 May 2016. Preliminary data were presented at the 2016 Annual Meeting of the Society for Melanoma Research and are summarized in Table 1.

Table 1. Study CMEK162B2301: Adverse Events, Regardless of Relationship to Study Drug(s), by Preferred Term – Overall and Maximum Grades 3 and 4 (> 25% in any treatment group, or Grade 3/4 AEs >5% in any treatment group; Safety Set, Part 1)

	Encorafenib 450 mg + Binimetinib 45 mg N =192		Encorafenib 300 mg N = 192		Vemurafenib N = 186	
Preferred Term	**All Grades %**	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**	**All Grades %**	**Grade 3/4 %**
Total	**98**	**58**	**99**	**66**	**99**	**63**
Nausea	41	2	39	4	34	2
Diarrhea	36	3	14	2	34	2
Vomiting	30	2	27	5	15	1
Fatigue	29	2	25	1	31	2
Arthralgia	26	1	44	9	45	6
Blood CK increased	23	7	1	0	2	0
Headache	22	2	27	3	19	1
Pyrexia	18	4	15	1	28	0
GGT increased	15	9	11	5	11	3
Alopecia	14	0	56	0	37	0
Hyperkeratosis	14	1	38	4	29	0
Dry skin	14	0	30	0	23	0
Myalgia	14	0	28	10	18	1
Rash	14	1	21	2	29	3
Hypertension	11	6	6	3	11	3
Palmoplantar keratoderma	9	0	26	2	16	1
Palmar-plantar erythrodysaesthesia syndrome	7	0	51	14	14	1

Abbreviations: AE = adverse event; GGT = gamma-glutamyltransferase; PT = preferred term
Preferred terms are presented by descending order based on frequency in the all patients all-grades column. A patient with multiple occurrences of an AE under a PT is counted only once for that PT. A patient with multiple AEs is counted only once in the total row.

2.5.2.3. Efficacy

In study CMEK162B2301 the primary objective was met as the combination of encorafenib and binimetinib significantly improved progression free survival (PFS) compared with vemurafenib. In addition, overall survival (OS) and confirmed overall response rates (ORR) were also improved in patients treated with the combination binimetinib compared to vemurafenib (Table 2).

Table 2. Efficacy Results for CMEK162B2301 Part 1

	BRAFTOVI with binimetinib N = 192	**Vemurafenib N = 191**
Progression-Free Survival		
Median PFS in months (95% CI)	14.9 (11.0, 18.5)	7.3 (5.6, 8.2)
HR (95% CI)[a]	0.54 (0.41, 0.71)	
P-value[b]	<0.0001	
Overall Survival		
Median OS in months (95% CI)	33.6 (22.4, 39.2)	16.9 (14.0, 24.5)
HR (95% CI)[a]	0.61 (0.47, 0.79)	
Confirmed Overall Response Rate by Central Assessment		
ORR (95% CI)	63% (56%, 70%)	40% (33%, 48%)
CR	8%	6%
PR	55%	35%
Duration of Response		
Median DoR in months (95% CI)	16.6 (12.2, 20.4)	12.3 (6.9, 16.9)

CI = Confidence interval; CR = Complete Response; HR = hazard ratio; NE = Not estimable; PFS = progression-free survival; PR = Partial response.

a Estimated with Cox proportional hazard model adjusted by the following stratification factors: American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

b Log-rank test adjusted by the same stratification factors.

Although the safety and efficacy of BRAF and MEK inhibitors have been established in patients with *BRAF*-mutant melanoma without prior exposure to these agents, there is clinical evidence that the combination of binimetinib and encorafenib is also active in patients who have received prior BRAF inhibitors. In an ongoing Phase 1b/2 study of encorafenib in combination with binimetinib (Study CMEK162X2110), in a cohort of 26 patients with *BRAF*-mutant melanoma who had received prior BRAF inhibitor treatment, confirmed responses were reported in 11 (42.3%) patients, including 1 complete response (CR). The disease control rate (CR + partial response [PR] + stable disease [SD]) was 73.1% in this

cohort. The duration of response and progression-free survival (PFS) in this cohort were both 3.8 months.

The data with binimetinib and encorafenib are consistent with recent retrospective analyses suggesting that *BRAF*-mutant tumors may be re-sensitized to targeted therapy following a drug holiday or after administration of a non-BRAF inhibitor therapy. Valpione and colleagues identified 116 patients with *BRAF*-mutant melanoma who were re-challenged with a range of BRAF and MEK inhibitors, including binimetinib and encorafenib, after a median 7.7 months following cessation of an initial BRAF inhibitor-containing regimen. A total of 31 (37%) patients who had progressed on prior BRAF inhibitor-containing therapy experienced a response (including 1 patient with a CR) when re-treated with targeted therapy (Valpione et al 2017). Collectively, these data suggest that in a portion of patients with *BRAF*-mutant melanoma, re-treatment with a BRAF/MEK inhibitor combination may offer clinical benefit.

2.6. Rationale

2.6.1. Rationale for the Study

Preclinical and clinical data suggest that the combination of a BRAF inhibitor and a MEK inhibitor may be more effective than BRAF inhibitor monotherapy in patients with *BRAF* mutant cancer. By simultaneous, dual, vertical pathway inhibition of the RAF/MEK/ERK signaling pathway, the combination of encorafenib and binimetinib may possibly improve the duration of response and delay the emergence of resistance to single-agent treatment in patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors.

This study is being conducted in patients with BRAF-mutant advanced solid tumors rather than in healthy volunteers due to its repeat-dose administration design and the risk of carcinogenicity (secondary neoplasm) with selective BRAF inhibitors (Zimmer et al 2012).

Data from in vitro studies indicated that encorafenib is mainly metabolized by CYP3A4, followed by CYP2C19 and CYP2D6, thus making encorafenib susceptible to DDI when coadministered with CYP inhibitors or inducers (for further details see Section 2.3.1.1.2). Encorafenib is a relatively potent reversible inhibitor of UGT1A1, CYP2B6, CYP2C9, and CYP3A4/5, and also a time-dependent inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Encorafenib was found to be a weak inhibitor of BCRP, and a potent inhibitor of renal transporters OCT2, OAT1, OAT3 and hepatic transporters OCT1, OATP1B1 and OATP1B3.

The main pathways of metabolism for binimetinib include glucuronidation by UGT1A1, UGT1A3 and UGT1A9 and to a lesser extent oxidation by CYP1A2 and CYP2C19 (for further details see Section 2.4.1.1.2). In vitro, binimetinib reversibly inhibits CYP2B6 and is a weak reversible inhibitor of CYP1A2 and CYP2C9. Binimetinib is not considered a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5. Binimetinib is a substrate of P-gp and BCRP.

No significant PK DDIs between encorafenib and binimetinib have been observed in clinical studies in oncology patients. However, the potential for DDIs of this combination with other agents has not been evaluated and this study is designed to contribute to that information by evaluating a probe cocktail containing key CYP isozymes of interest (CYP3A4, CYP2C19, CYP2D6, CYP1A2, CYP2C9), a OATP/BCRP substrate, a CYP2B6 substrate and a moderate CYP3A4 inducer. However, given the nonclinical data, it is unlikely that binimetinib would have relevant contribution to any clinical DDI observed.

In Arm 1 of this study, the effect of encorafenib in combination with binimetinib on the single oral dose PK of specific CYP isozymes substrates will be assessed. The "Inje" probe cocktail was selected as it includes losartan (CYP2C9), midazolam (CYP3A4), caffeine (CYP1A2), omeprazole (CYP2C19), and dextromethorphan (CYP2D6), which are all CYP substrates of interest to coadministration with encorafenib (Ryu 2007).

In Arm 2 of this study, the effect of encorafenib in combination with binimetinib on the single oral dose PK of an OATP/ BCRP substrate and a CYP2B6 substrate will be assessed. Rosuvastatin was chosen as the OATP/ BCRP substrate of interest as it is not known to inhibit or induce any CYPs relevant to encorafenib metabolism (Causevic-Ramosevac 2013; Neuvonen 2006). Bupropion was chosen as the CYP2B6 substrate of interest as it is considered a sensitive substrate (Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers) and no interaction with rosuvastatin is expected (bupropion hydrochloride prescribing information; rosuvastatin calcium prescribing information).

In Arm 3 of the study, the effect of repeat doses of a moderate CYP3A4 inducer on the repeat dose PK of CYP3A4 substrate encorafenib will be assessed. Modafinil was chosen as the CYP3A4 inducer as it is considered a moderate inducer (Food and Drug Administration, Guidance for Industry 2012). The effect of modafinil (200 mg for 7 days followed by 400 mg for 21 days) on CYP3A4 substrate triazolam PK was moderate, with a 59% decrease on mean AUC_{inf} (Robertson et al. 2002). Based on the similarity of the observed DDI with oral CYP3A4 substrate midazolam from a cocktail study (Rowland et al. 2018) with modafinil (200 mg modafinil for 7 days with single 1 mg midazolam dose as probe, AUC ratio of 0.66), and from a DDI study (Darwish et al. 2008) of armodafinil (R-modafinil, 250 mg for 32 days with single 5 mg midazolam dose as probe, AUC ratio of 0.66), 7 days is a sufficient period of coadministration for induction. Modafinil has been shown to be well tolerated with the only AE observed in >15% of patients is headache (Roth et al. 2007).

The study will be conducted in 3 arms to mitigate any unknown interaction between the substrates and inducer.

2.6.2. Rationale for Dose Selection

Dosing for encorafenib (450 mg once daily [QD]) in combination with binimetinib (45 mg BID) in this study is consistent with the dosing the regimen used in the registrational study, CMEK162B2301 and therefore most appropriate to assess possible DDIs. In previous studies, these doses have been shown to be clinically active with an acceptable safety profile in patients with BRAF-mutated locally advanced unresectable or metastatic melanoma. Notably, based on preliminary data, BRAF inhibitor target toxicities such as hand foot skin

reaction, hyperkeratosis, arthralgia, myalgia, and fatigue that are frequently observed with encorafenib single agent, were reduced by the combination with binimetinib.

The CYP probe cocktail drugs will be administered at the dose closest to, or lower than, the doses referenced in the Inje cocktail paper (Ryu 2007). Rosuvastatin will be administered at the initial recommended starting dose of 10 mg. Bupropion will be administered at the lowest commercially available dose. For modafinil PK, steady state is achieved after approximately 2-4 days of dosing (modafinil prescribing information). Modafinil will be administered at 400 mg for 7 days to ensure sufficient time for CYP3A4 induction (Rowland 2018), while minimizing the time for which patients may have reduced exposures to encorafenib.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

All objectives pertain to the DDI phase of the study only.

3.1.1. Primary Objectives

- To evaluate the effect of single and multiple oral doses of encorafenib in combination with binimetinib on the single oral dose PK of the CYP enzyme probe substrates, losartan (CYP2C9), midazolam (CYP3A4), caffeine (CYP1A2), omeprazole (CYP2C19), and dextromethorphan (CYP2D6) and selected metabolites, in patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors.
- To evaluate the effect of single and multiple oral doses of encorafenib in combination with binimetinib on the single oral dose PK of rosuvastatin, an OATP /BCRP substrate, and on the single oral dose PK of bupropion (a CYP2B6 substrate) and hydroxybupropion, in patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors.
- To evaluate the effect of multiple doses of modafinil, a moderate CYP3A4 inducer, on the multiple oral dose PK of encorafenib and its metabolite, LHY746, in patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors.

3.1.2. Secondary Objectives

- To assess the single and multiple dose PK of encorafenib, LHY746 and binimetinib (and its metabolite, AR00426032) after coadministration with a single oral dose of the CYP probe cocktail, rosuvastatin and bupropion.
- To assess the safety and tolerability of single and multiple oral doses of encorafenib in combination with binimetinib when administered with a single oral dose of the CYP probe cocktail, rosuvastatin and bupropion during the DDI portion of the study.
- To assess safety and tolerability of multiple oral doses of encorafenib in combination with binimetinib when administered with multiple doses of modafinil during the DDI portion of the study.

CCI

[redacted]

3.2. Study Endpoints

3.2.1. Primary Endpoint

- Changes in plasma maximum concentration (C_{max}) and area under the concentration time curve from time zero to the time of last quantifiable concentration (AUC_{last}): midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxy omeprazole, rosuvastatin, bupropion and hydroxybupropion.

- Changes in the amount eliminated via urine over an 8-hour period (Ae_{0-8}): losartan and its metabolite (E-3174), dextromethorphan and dextrorphan
- Changes in plasma encorafenib and LHY746 C_{max} and area under the concentration time curve over the dosing interval (AUC) in Arm 3.

3.2.2. Secondary Endpoints

- Metabolite ratios (MR_{AUC} and MR_{Cmax}) for 1-OH midazolam/midazolam, paraxanthine/caffeine, 5-hydroxy omeprazole/omeprazole, hydroxybupropion/bupropion and LHY746/encorafenib and MR_{Ae0-8} for E-3174/losartan and dextrorphan/dextomethorphan.
- Pharmacokinetic parameters (e.g., time to reach C_{max} [T_{max}], AUC from time zero extrapolated to infinity [AUC_{inf}], percent of AUC extrapolated [$AUC_{\%extrap}$], apparent terminal elimination rate constant [Kel], apparent $T_{1/2}$, apparent total body clearance after extravascular administration [CL/F] and apparent total volume of distribution after extravascular administration [V_z/F]) where calculable, for midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxyomeprazole, rosuvastatin, bupropion and hydroxybupropion.
- Pharmacokinetic parameters (e.g., urine concentration [C_{urine}], quantity of urine excreted during each collection interval [Vol], cumulative amount excreted in urine during each collection interval [$CumA_e$], and percentage of dose recovered in urine [Fe %]) for losartan, E-3174, dextromethorphan and dextrorphan.
- Pharmacokinetic parameters (e.g., C_{max}, AUC_{last}, T_{max}, AUC_{inf}, $AUC_{\%extrap}$, Kel, $T_{1/2}$, CL/F, and V_z/F) for encorafenib, LHY746, binimetinib and AR00426032 where calculable.
- Safety will be evaluated by monitoring AEs, physical examinations, ophthalmic examinations, vital sign measurements, 12-lead ECGs, echocardiogram (ECHO)/multigated acquisition scan (MUGA), and clinical laboratory tests.

CCI [redacted]

4. STUDY DESIGN

4.1. Study Design Overview

This is an open-label, 3-arm, fixed-sequence study to evaluate the effect of single and multiple oral doses of encorafenib in combination with binimetinib on the single oral dose PK of CYP enzyme probe substrates using a probe cocktail, on an OATP/BCRP substrate using rosuvastatin and on a CYP2B6 substrate using bupropion. In addition, this study will evaluate the effect of multiple doses of modafinil, a moderate CYP3A4 inducer, on the multiple oral dose PK of encorafenib.

The study will have 2 treatment phases, a DDI phase followed by a post-DDI phase. During the DDI phase patients will receive the CYP probe drug cocktail (Arm 1), the OATP/BCRP probe substrate, rosuvastatin and CYP2B6 substrate, bupropion (Arm 2), or the CYP3A4 inducer, modafinil (Arm 3) and encorafenib in combination with binimetinib.

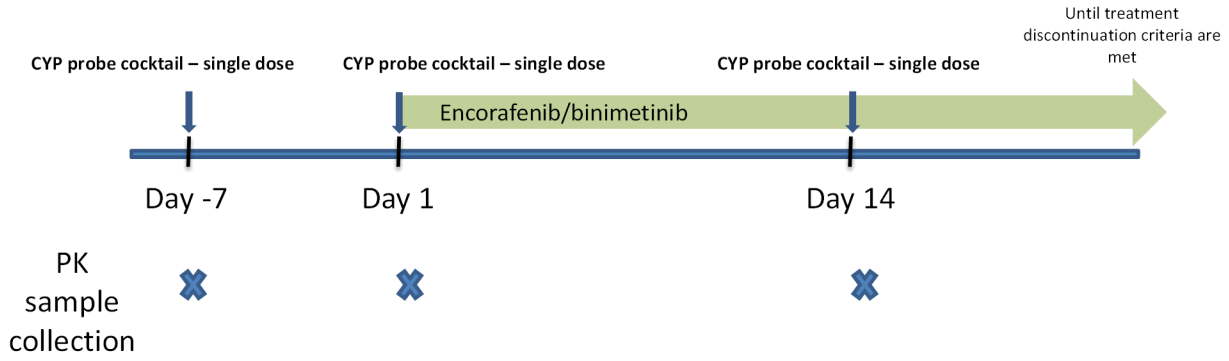
During the post-DDI phase patients may continue to receive treatment with encorafenib in combination with binimetinib until treatment discontinuation criteria are met (see Section 9.1). The combination of encorafenib 450 mg QD and binimetinib 45 mg BID has been evaluated in over 300 patients with *BRAF* V600 mutant melanoma in previous studies including 192 patients in the pivotal Phase 3 trial, CMEK162B2301. Since the safety and efficacy of the combination has already been extensively studied in previous trials, in the post-DDI phase of the current trial, patients will be followed as per local standard-of-care practice for patients with *BRAF* V600-mutant unresectable or metastatic melanoma or other advanced solid tumors and only limited data will be collected (see Section 8.3.4). The follow-up in the post-DDI phase will include a review of concomitant medications and assessment of compliance with administration of encorafenib and binimetinib. There will also be review of AEs with recording of all Grade 3 or 4 AEs and all SAEs (SAEs, follow-up of SAEs to continue as described in Section 10.1.5). Other safety evaluations may be conducted if clinically indicated.

4.1.1. DDI Phase

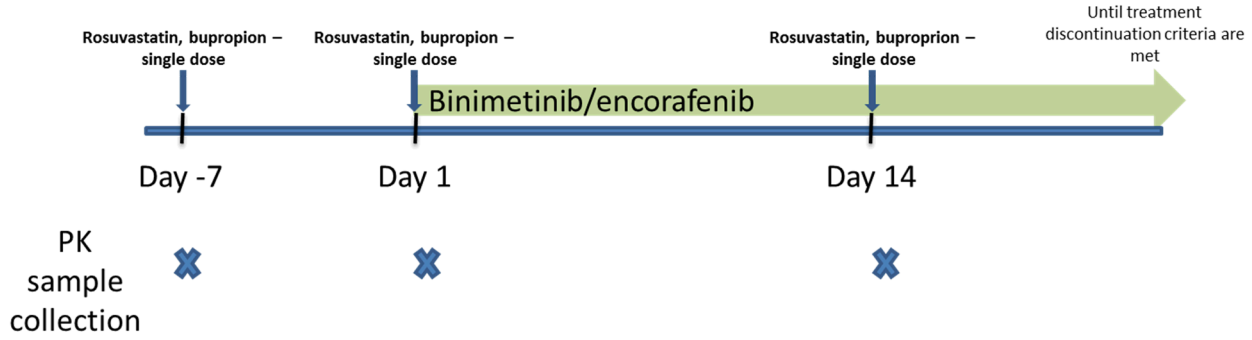
Enrollment to Arms 1 and 2 will occur in parallel. Patients will be assigned to the appropriate treatment arm by the Sponsor study team based on eligibility. Enrollment to Arm 3 will begin once Arm 2 enrollment is complete. The study schema for each Arm are presented in Figure 1.

Figure 1: Study Schema

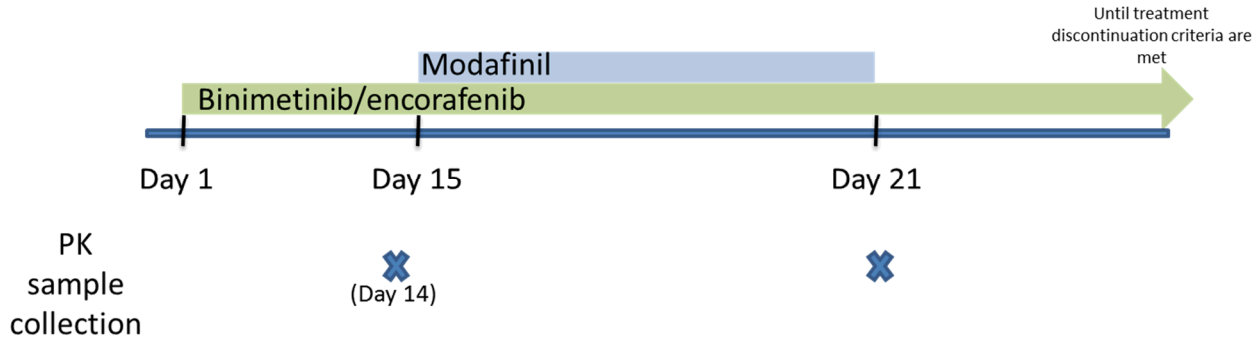
Arm 1 (CYP Probe Cocktail)



Arm 2 (Rosuvastatin and Bupropion)



Arm 3 (Modafinil)



In Arm 1, patients will receive a single oral dose of the CYP probe cocktail on Day -7. Encorafenib, administered 450 mg QD and binimetinib, administered 45 mg BID will be initiated on Day 1. Patients will then receive a single oral dose of the CYP probe cocktail Day 1 and Day 14 within 5 minutes after the encorafenib/binimetinib administration. Blood and urine PK sampling will be conducted from 0 to 8 hours on Day -7, Day 1 and Day 14.

In Arm 2, patients will receive a single oral dose of rosuvastatin and bupropion on Day -7. Encorafenib, administered 450 mg QD and binimetinib, administered 45 mg BID will be

initiated on Day 1. Patients will then receive a single oral dose of rosuvastatin and bupropion on Day 1 and Day 14 within 5 minutes after the encorafenib/binimetinib administration. Blood PK sampling will be conducted from 0 to 8 hours on Day -7, Day 1 and Day 14.

In Arm 3, patients will inititate continuous treatment with encorafenib 450 mg QD and binimetinib 45 mg BID on Day 1. Patients will then receive continuous treatment of modafinil on Day 15 through Day 21. Blood PK sampling will be conducted from 0 to 8 hours on Day 14 and Day 21.

Patients who discontinue or require a dose reduction of study drug(s), in particular encorafenib, prior to completion of the last PK sampling on Day 14 in Arms 1 and 2 or on Day 21 in Arm 3 may be considered unevaluable for PK analyses and may be replaced. If a patient misses 3 or more consecutive doses of encorafenib in any arm or 3 or more consecutive doses of modafinil in Arm 3 prior to completion of the last PK sampling on Day 14 in Arms 1 and 2 or on Day 21 in Arm 3 due to noncompliance, the patient may remain on treatment but may be replaced if limited data are available from the patient. In addition, patients who miss any dose of study drugs on any of the PK days, or who vomit within 4 hours after dosing on any of the PK days, may be replaced but may remain on treatment.

4.1.2. Post-DDI Phase

During the post-DDI phase patients may continue to receive treatment with the encorafenib/binimetinib combination until one of the treatment discontinuation reasons described in Section 9.1 occur (e.g., until disease progression, unacceptable toxicity, withdrawal of consent, pregnancy, significant protocol deviation, lost to follow up, Investigator decision, death, or study termination by Sponsor). Patients should be followed by the Investigator per standard clinical practice and all Grade 3-4 AEs and all SAEs should be reported to the Sponsor (see Section 8.3.4). If a patient chooses to not continue in the post-DDI phase, the Day 30 Safety Follow-up Visit assessments will be performed.

If a patient in the post-DDI phase permanently discontinues treatment with binimetinib, they may continue treatment with encorafenib as monotherapy at its RP2D the dose of 300 mg QD. However, due to the limited efficacy of binimetinib alone in the study population, if a patient permanently discontinues treatment with encorafenib, they must discontinue treatment with binimetinib and complete the Day 30 Safety Follow-up Visit.

4.2. Doses and Schedule of Administration

4.2.1. Treatment Regimens

Encorafenib/binimetinib (continuous daily dosing starting on Day 1 for all arms):

- 450 mg (6 x 75 mg) encorafenib oral capsule QD
- 45 mg (3 x 15 mg) binimetinib oral tablet BID

Encorafenib and binimetinib are to be taken together 5 minutes before the CYP probe cocktail (Arm 1), rosuvastatin and bupropion (Arm 2) or modafinil (Arm 3) on days when all study drugs are administered together.

Patients will be supplied with a sufficient number of tablets and/or capsules for the number of doses to be taken prior to the next scheduled visit. In addition, patients will be provided a dosing diary and should document in this diary each prescribed dose, and whether it was taken or not.

Patients should be instructed to take encorafenib and binimetinib with ~250 mL of noncarbonated water at room temperature daily at approximately the same time every day. Patients should be instructed to swallow the capsules/tablets whole and not to chew or crush them. The prescribed dose for encorafenib should be taken once daily in the morning at approximately the same time every day. The prescribed doses for binimetinib should be taken twice daily, approximately 12 ± 2 hours apart.

Consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each starting from Day -14 through the DDI phase (Day 28) is prohibited, due to potential CYP3A4 interaction with the study drugs (see Section 5.4.2.1). Orange juice is allowed.

On all PK days during the DDI phase of the study, patients should not eat anything within 2 hours prior to the morning dose(s) of study drug intake and refrain from eating for 1 hour following encorafenib and binimetinib intake. During the remainder of the study, the afternoon/evening doses of binimetinib may be taken with or without a meal but the same method should be used consistently throughout the study. Encorafenib and binimetinib may be taken with or without food on non-PK days.

On visit days when the patient is scheduled to be at the clinic, patients will take encorafenib and binimetinib in the clinic under the supervision of the Investigator or designee in the morning. On the evening of the visit day patients will take binimetinib at home. On all other days patients will take encorafenib and binimetinib at home.Doses of encorafenib that are omitted for AEs or any other reason can be taken up to 12 hours prior to the next dose. Doses of binimetinib that are omitted for AEs or any other reason should not be made up. If a patient misses 3 or more consecutive doses of encorafenib and binimetinib in any arm or 3 or more doses of modafinil in Arm 3 during the DDI phase due to noncompliance, the patient may remain on treatment but may be replaced if limited data are available from the patient (see Section 9.2). In addition, patients who miss a dose of study drugs on any of the PK days and patients who vomit within 4 hours after dosing on any of the PK days may be replaced but may remain on treatment. If a patient vomits at any time after dosing, the dose of study drug should not be re-administered.

Complete dosing instructions will be provided to patients and will include the minimum times between doses and instructions for missed doses. The Investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes and all missed doses during the study must be recorded on the Dosage Administration Record electronic case report form (eCRF). Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at each evaluation visit. The site personnel will ensure that the appropriate dose of each study drug is

administered at each visit and will provide the patient with the correct amount of drugs for subsequent dosing.

CYP Probe Cocktail (once on Day -7, Day 1 and Day 14 for Arm 1 only) taken in the following order:

- 25 mg losartan oral tablet
- 30 mg dextromethorphan oral capsule
- 50 mg caffeine as oral liquid
- 20 mg omeprazole oral capsule
- 2 mg midazolam as oral syrup

The CYP probe cocktail will be administered in the clinic. The CYP probe cocktail is to be taken approximately 5 minutes after administration of encorafenib and binimetinib on days when all study drugs are administered. The total time for administration of all study drugs should be within 10 minutes.

The actual dose time for each drug will be recorded. Time 0 will be the time that the first drug is taken. None of the oral drugs with solid dose forms should be chewed. Each oral administration should be confirmed by checking the oral cavity of the patient. A glass with 250 mL of water (room temperature) should be available to take the oral doses. Any remaining water after finishing all dosing should be consumed if possible.

Rosuvastatin and bupropion (Day -7, Day 1 and Day 14 for Arm 2 only):

- 10 mg rosuvastatin oral tablet
- 75 mg bupropion immediate release (IR) oral tablet

Rosuvastatin and bupropion doses will be administered in the clinic and are to be taken approximately 5 minutes after administration of encorafenib and binimetinib on days when all study drugs are administered. The total time for administration of all study drugs should be within 10 minutes.

The actual dose time for each drug will be recorded. Time 0 will be the time that the first drug is taken. These solid dose forms should not be chewed. Each oral administration should be confirmed by checking the oral cavity of the patient. A glass with 250 mL of water (room temperature) should be available to take the oral doses. Any remaining water after finishing all dosing should be consumed if possible.

Modafinil (continuous daily dosing starting on Day 15 through Day 21 for Arm 3 only):

- 400 mg modafinil as oral tablet(s) QD

Patients will be supplied with a sufficient number of tablets for the number of doses to be taken prior to the next scheduled visit. In addition, patients will be provided a dosing diary and should document in this diary each prescribed dose, and whether it was taken or not.

Patients should be instructed to take encorafenib and binimetinib with ~250 mL of noncarbonated water at room temperature daily at approximately the same time every day. Patients should be instructed to swallow the tablets whole and not to chew or crush them. The prescribed dose for modafinil should be taken once daily in the morning at approximately the same time every day. Modafinil may be taken with or without food on non-PK days.

On visit days when the patient is scheduled to be at the clinic, patients will take modafinil in the clinic under the supervision of the Investigator or designee in the morning. On all other days patients will take modafinil at home.

Complete dosing instructions will be provided to patients and will include the minimum times between doses and instructions for missed doses. The Investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes and all missed doses during the study must be recorded on the corresponding electronic case report form (eCRF). Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at each evaluation visit. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drugs for subsequent dosing.

4.3. Duration of Treatment

Prescreening:

Prescreening evaluations must be performed between Day -57 and Day -36 in Arms 1 and 2 and between Day -50 and Day -29 in Arm 3.

Screening:

Screening of patients will occur within 28 days prior to the first study drug dose on Day -7 (Day -35 to Day -8, inclusive) in Arms 1 and 2 and prior to the first study drug dose on Day 1 (Day -28 to Day -1, inclusive) in Arm 3.

DDI Phase:

The duration of the DDI phase will be 35 days in Arms 1 and 2 and will include clinic visits on Day -7, Day 1, Day 14, and Day 28. The duration of the DDI phase will be 28 days in Arm 3 and will include clinic visits on Day 1, Day 14, Day 15, Day 21 and Day 28.

Post-DDI Phase:

Patients will be followed by the Investigator following standard clinical practice and may continue to receive study treatment as long as none of the treatment discontinuation criteria are met (Section 9.1).

5. PATIENT POPULATION

During the COVID-19 pandemic, please refer to Appendix 13 for additional eligibility considerations.

5.1. Number of Patients

Up to approximately 42 patients with unresectable or metastatic *BRAF* V600-mutant cancer are planned for enrollment; 20 patients in Arm 1,10 patients in Arm 2 and up to 12 patients in Arm 3.

5.2. Selection of Patients

Questions regarding patient eligibility should be addressed to the Sponsor prior to enrollment. Patients must fulfill all of the following inclusion criteria and none of the exclusion criteria to be eligible for admission to the study.

5.2.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for enrollment in the study.

1. Signed written informed consent;
2. Male or female patient, age ≥ 18 years;
3. Histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma or unknown primary melanoma American Joint Committee on Cancer (AJCC) Stage IIIB, IIIC or IV, or other *BRAF* V600-mutant advanced solid tumors;
4. Presence of *BRAF* V600E and/or V600K mutation in tumor tissue prior to enrollment, as determined using a local test;
5. Evidence of measurable or non-measurable lesions as detected by radiological or photographic methods according to guidelines based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 7);
6. Patient with unresectable locally advanced or metastatic melanoma who has received no prior treatment or progressed on or after other prior systemic therapy

   Note: Prior therapy with a BRAF inhibitor (e.g., vemurafenib, dabrafenib, encorafenib and XL281/BMS-908662) and/or a MEK inhibitor (e.g., trametinib, binimetinib, selumetinib, cobimetinib and refametinib) is permitted except in the regimen immediately prior to study entry. Progression during prior BRAF/MEK inhibitor treatment is not required;
7. Patient with other (non-melanoma) *BRAF* V600E and/or V600K -mutant advanced solid tumors who has progressed on standard therapy or for whom there are no available standard therapies

   Note: Prior therapy with a BRAF inhibitor and/or a MEK inhibitor is permitted except in the regimen immediately prior to study entry. Progression during prior BRAF/MEK inhibitor treatment is not required; if it occurred, the patient's circumstances (e.g., ≥ 1 year since prior BRAF and/or MEK inhibitor, equivocal progression,

refractory to available therapies) must be discussed with the Sponsor prior to enrollment;

8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1;
9. Adequate bone marrow, organ function and laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    b. Hemoglobin (Hgb) ≥ 9 g/dL without transfusions
    c. Platelets (PLT) ≥ 100 x 10^9/L without transfusions
    d. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN); patient with liver metastases ≤ 5 ×ULN
    e. Total bilirubin ≤ 2 × ULN
    f. Creatinine ≤ 1.5 mg/dL, or calculated creatinine clearance (determined as per Cockcroft-Gault) ≥ 50 mL/min;
10. Able to take oral medications;
11. Patient is deemed by the Investigator to have the initiative and means to be compliant with the protocol (treatment and follow-up);
12. Negative serum beta-human chorionic gonadotropin (β-HCG) test (female patient of childbearing potential only) performed within 72 hours prior to first dose and consent to ongoing urine pregnancy testing during the course of the study;
13. Male patients and female patients of childbearing potential must agree to use an acceptable method of contraception as defined in the study protocol (Section 5.3.1).

ARM 1 ONLY:

1. Non-smoker who has not used nicotine containing products for at least 3 months prior to the first dose.

5.2.2. Exclusion Criteria

Patients meeting any of the following criteria are ineligible for enrollment in the study.

1. Symptomatic brain metastasis. Patients previously treated or untreated for these conditions who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable, with imaging (e.g., magnetic resonance imaging [MRI] or computed tomography [CT] demonstrating no current evidence of progressive brain metastases at screening);
2. History of reaction to any of the study medications in the arm the patient is enrolled in this trial;
3. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any herbal medications/supplements or any medications or foods that are moderate or strong inhibitors or inducers of CYP 3A4/5;

4. Consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each starting starting from Day -14 and through DDI phase (Day 28), due to potential CYP3A4 interaction with the study drugs (see Section 5.4.2.1). Orange juice is allowed;

5. Symptomatic or untreated leptomeningeal disease;

6. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes);

7. Clinically significant cardiac disease including any of the following:
    a. Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2)
    b. Left ventricular ejection fraction (LVEF) < 50% as determined by MUGA or ECHO
    c. Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy
    d. History or presence of clinically significant ventricular arrhythmias or atrial fibrillation
    e. Clinically significant resting bradycardia
    f. Unstable angina pectoris ≤ 3 months prior to start of study drug
    g. Acute myocardial infarction ≤ 3 months prior to start of study drug
    h. QT interval corrected for heart rate using the Fridericia formula (QTcF) > 480 msec at screening;

8. Impaired hepatic function as defined by Child-Pugh class B or C (Appendix 8);

9. Impaired gastrointestinal function or disease which may significantly alter the absorption of study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection);

10. Known hyper-coagulability risks other than malignancy (e.g., Factor V Leiden syndrome);

11. Thromboembolic event (e.g. including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli) except catheter-related venous thrombosis ≤ 12 weeks prior to starting study treatment. ***Note:*** Patients with catheter-related thromboembolic events are allowed.;

12. Any of the following:
    a. Nitrosourea or mitomycin-C within 6 weeks prior to start of study drug
    b. Other chemotherapy, radiation therapy that included > 30% of the bone marrow reserve, or biological therapy (e.g., antibodies) within 4 weeks prior to start of study drug
    c. Continuous or intermittent small-molecule therapeutics or investigational agents within 5 half-lives of the agent (or within 4 weeks prior to start of study drug, when half-life is unknown)

d. Residual Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 side effects of any such therapy (residual Grade 2 alopecia is permitted);

13. Discontinuation of prior BRAF and/or MEK inhibitor treatment due to left ventricular dysfunction, pneumonitis/interstitial lung disease, or retinal vein occlusion;
14. Known positive serology for human immunodeficiency virus (HIV) infection, active hepatitis B and/or active hepatitis C infection;
15. History of Gilbert's syndrome;
16. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgement of the Investigator, would make the patient inappropriate for the study;
17. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until termination of gestation, confirmed by a positive β-hCG laboratory test (> 5 mIU/mL).

ARM 1 ONLY:

1. Positive urine cotinine test at screening;
2. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP3A4, CYP2C9, CYP1A2 or CYP2C19 and any substrates or inhibitors of CYP2D6

ARM 2 ONLY:

1. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP2B6 or any substrates or inhibitors of BCRP, OATP1B1 or OATP1B3.

ARM 3 ONLY:

1. History of psychosis, depression or mania;
2. History of angioedema;
3. History of mitral valve prolapse;
4. History of left ventricular hypertrophy;
5. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP3A4.

5.3. Lifestyle Guidelines

5.3.1. Requirements for Contraception

Females of non-childbearing potential (study patients or partners of study patients) are not required to use contraception. To be considered of non-childbearing potential, a female patient must meet at least one of the following criteria:

- Postmenopausal (defined as without menses for at least 12 consecutive months before screening) AND at least 55 years old
- Postmenopausal (defined as without menses for at least 12 consecutive months before screening) AND a follicle-stimulating hormone (FSH) value > 30 IU/L at the Screening Visit
- Hysterectomy OR bilateral oophorectomy
- Tubal ligation at least 5 years prior to the Screening Visit with no subsequent pregnancies.

Contraception must be used starting at screening for males and females of childbearing potential. Use must continue for 90 days after the last dose of study drug for males and 30 days after the last dose of study drug for females. The following methods of contraception have been determined to be effective and acceptable per Clinical Trial Facilitation Group (CTFG) guidance and are mandated under this protocol for use by the patient and his/her partner:

- Complete abstinence from sexual intercourse when this is in line with the preferred and usual lifestyle of the patient
- Double barrier methods
    - Condom with spermicide in conjunction with use of an intrauterine device
    - Condom with spermicide in conjunction with use of a diaphragm
- Birth control patch or vaginal ring
- Oral, injectable, or implanted contraceptives only when combined with other highly effective or acceptable methods
    - This is required due to the potential of encorafenib to induce CYP3A4 which may reduce the effectiveness of hormonal contraception methods, hormonal agents (including but not limited to birth control patch, vaginal ring, oral, injectable, or implanted contraceptives)
- Surgical sterilization (bilateral oopherectomy with or without hysterectomy, tubal ligation or vasectomy) at least 6 weeks prior to taking study treatment. In the case of

oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up levels of FSH.

5.3.2. Ultaviolet Light Exposure

Photosensitivity was reported infrequently in patients treated with encorafenib (2.9% - 5.6% in single-agent Study CLGX818X2101 Expansion Phase). However, it is recommended that patients use precautionary measures against ultraviolet exposure from the first day of study drug treatment through the last day of study drug treatment. It is recommented that patients avoid extended exposure to ultraviolet light and when out of doors, to wear occlusive clothing, sunscreen, and sunglasses.

5.4. Prior and Concomitant Medications

5.4.1. Prior Treatments

All prior cancer treatments are to be recorded in the eCRF. Other prior treatments (i.e., other than cancer treatments) taken within 4 weeks of screening should also be recorded.

5.4.2. Concomitant Medications

During the DDI phase of the study, all medications (other than study drugs) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Surgical and Medical Procedures eCRF.

5.4.2.1. Prohibited Concomitant Medications

Please refer to Appendix 6 for a list of prohibited medications.

Anticancer therapies (including chemo- or biologic-therapy or radiation therapy, covering >30% of the red bone marrow reserve, and surgery) are prohibited while the patients are receiving study treatment. If such therapeutic measures are required for a patient then the patient must be discontinued from study treatment.

For all Arms of the study, from Day 1 and through the DDI phase (Day 28) of the study, the use of any herbal medications/supplements or any medications or foods that are moderate or strong inhibitors or inducers of CYP 3A4/5. Other prohibited medications specific to each study arm are specified below:

- Arm 1: Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP3A4, CYP2C9, CYP1A2 or CYP2C19 and any substrates or inhibitors of CYP2D6.

- Arm 2: Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP2B6 or any substrates or inhibitors of BCRP or OATP.

- Arm 3: Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP3A4.

Consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each starting from Day -14 through the DDI phase (Day 28) is prohibited, due to potential CYP3A4 interaction with the study drugs. Orange juice is allowed.

During the DDI phase of the study, drinks and food containing caffeine must be excluded 48 hours before PK assessments and the day of PK assessments (i.e., Days -9 to -7, -2 to 1, 12 to 14 for Arms 1 and 2 and Days 12 to 14 and Days 19 to 21 for Arm 3).

5.4.2.2. Permitted Concomitant Medication

The patient must notify the investigational site about any new medications he/she takes after the start of the study drug. Patients taking concomitant medications chronically should maintain the same dose and dose schedule throughout the study if medically feasible.

On the days PK blood sampling is performed, the patient should continue their consistent use of other concomitant medication. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on these days, if medically feasible.

Apixaban when used for thromboprophylaxis has been shown to result in a significantly lower rate of venous thromboembolism than placebo in ambulatory cancer patients with intermediate-to-high risk based on a Khorana score ≥2 who were starting chemotherapy. During the treatment period, major bleeding occurred in 2.1% of the patients treated with apixaban (versus 1.1% of patients who received placebo) with higher rates of gastrointestinal bleeding, hematuria, and gynecological bleeding. Patients with gastrointestinal or gynecological cancers had the highest rates of bleeding. There was no significant difference in overall survival between the apixaban-treated and placebo-treated patients in the study (Carrier 2019). The Investigator should assess the potential benefit/risk to the patient and determine whether it is in the patient's best interest to initiate thromboprophylaxis

5.4.2.3. Permitted Concomitant Medication Requiring Caution and/or Action

Please refer to Appendix 6 for a list of permitted medications to be used with caution.

During the post-DDI phase of the study, the following guidance on permitted concomitant therapy will apply:

Encorafenib is a reversible inhibitor of CYP2B6, CYP2C9, CYP3A4 and UGT1A1. It is also a time dependent inhibitor of CYP3A4. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2B6, CYP2C9, CYP3A4, and UGT1A1 or those substrates that have a narrow therapeutic index (NTI).

There is a potential for encorafenib to induce CYP3A4 at concentrations >10-50 μM, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least one form of non-hormonal contraception will be needed during the participation in this

study. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib.

Encorafenib has been identified to be primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19 in vitro. The use of strong inhibitors of CYP3A4 are prohibited throughout the study. Concomitant use of moderate CYP3A4 inhibitors after the DDI phase of the study should be avoided. If use of a moderate CYP3A4 inhibitor is unavoidable, short-term use (≤ 30 days) following discussion with the Sponsor may be permitted with an accompanying dose reduction to one-half of the encorafenib dose prior to use of the moderate CYP3A4 inhibitor. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor. Moderate inhibitors of CYP3A4 should be taken with caution when co-administered with encorafenib. Patients should be closely monitored for the occurrence of AEs. Regular assessments will be performed as described in Table 7 and Table 8. If a patient develops toxicity, encorafenib dose may be adjusted as outlined in the dose modification Table 5.

In vitro data showed that both encorafenib and binimetinib are substrates of P-gp. Binimetinib is also a substrate of BCRP. Thus, the use of drugs that are known to inhibit or induce P-gp and BCRP should be used with caution. Encorafenib is a BCRP inhibitor. It is also a potent inhibitor of the renal transporters OAT1, OAT3 and OCT2 and the hepatic transporters OATP1B1 and OATP1B3. Therefore the co-administration of drugs that are known to be sensitive or NTI substrate of BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 should be used with caution.

Drugs with a conditional, possible, or known risk to induce Torsade de Pointes (TdP) should be used with caution. Patients receiving such medications must be carefully monitored for potentiating of toxicity due to any individual concomitant medication, and may require dose titration of the drug substance. Investigators should use caution when prescribing co-medications, as clinical experience with these compounds in patients with cancer is often limited. Investigators should contact the Sponsor when they are unsure whether a drug should be prescribed to a patient in the clinical trial.

Please refer to Appendix 6 for a list of permitted medications to be used with caution.

6. STUDY TREATMENT

The term "study drug" is defined as all components of the CYP probe cocktail, rosuvastatin, bupropion, modafinil, encorafenib or binimetinib.

6.1. Dosing Regimen

Treatments are described as follows (see Section 4.2):

CYP Probe Cocktail (once on Day -7, Day 1 and Day 14 for Arm 1 only) taken in the following order:

25 mg losartan oral tablet
30 mg dextromethorphan oral capsule

50 mg caffeine as oral liquid

20 mg omeprazole oral capsule

2 mg midazolam as oral syrup

Rosuvastatin and bupropion (once on Day -7, Day 1 and Day 14 for Arm 2 only):

10 mg rosuvastatin oral tablet

75 mg bupropion immediate release (IR) oral tablet

Modafinil (continuous daily dosing starting on Day 15 through Day 21 for Arm 3 only):

400 mg modafinil as oral tablet(s) QD

Binimetinib/encorafenib (continuous daily starting on Day 1 for all Arms):

450 mg (6 x 75 mg) encorafenib oral capsules QD

45 mg (3 x 15 mg) binimetinib oral tablet BID

6.2. Allocation to Treatment

Enrollment to Arms 1 and 2 will occur in parallel. Patients will be assigned to the appropriate treatment arm by the Sponsor study team based on eligibility. For example, a smoking patient would not be allowed to enroll in Arm 1. As there are multiple centers participating, the site must contact the study manager, or delegate, and receive the dosing assignment for each patient. Enrollment to Arm 3 will begin once Arm 2 enrollment is complete.

Twenty patients will be enrolled into Arm 1. Patients will receive a single oral dose of the CYP probe cocktail (losartan, dextromethorphan, caffeine, omeprazole, and midazolam) on Day -7. Encorafenib QD and binimetinib BID will be initiated on Day 1. Patients will then receive a single oral dose of the CYP probe cocktail on Day 1 and Day 14 within 5 minutes of the encorafenib/binimetinib administration.

Ten patients will be enrolled in Arm 2. Patients will receive a single oral dose of rosuvastatin and bupropion on Day -7. Encorafenib QD and binimetinib BID will be initiated on Day 1. Patients will then receive a single oral dose of rosuvastatin and bupropion on Day 1 and Day 14 within 5 minutes after the encorafenib/binimetinib administration.

Once enrollment to Arms 1 and 2 is completed, the next 6 to 12 patients will be enrolled in Arm 3. Patients will inititate continuous treatment with encorafenib QD and binimetinib BID on Day 1. Patients will then begin receiving continuous treatment of modafinil QD on Day 15 through Day 21.

6.3. Study Drug Supply

6.3.1. Packaging and Labeling

Encorafenib and binimetinib will be supplied centrally. Agents in the CYP probe cocktail, rosuvastatin, bupropion and modafinil will be supplied centrally.

Encorafenib and binimetinib will be packaged in high-density polyethylene (HDPE) containers, induction sealed and include child-resistant closures. For both encorafenib and binimetinib, each bottle will be labelled, at a minimum, with a lot number, contents (number of tablets), dosage strength, storage conditions, and the name and address of the Sponsor. Medication labels for encorafenib and binimetinib will be in the local language and comply with the legal requirements of each country. The patient number should be hand-written by the Investigator or its staff at the drug delivery time.

The CYP probe cocktail, rosuvastatin, bupropion, and modafinil will be sourced separately for United States and Canada/European sites. All labels will be in the local language and comply with the legal requirements for each country.

6.3.2. Shipping, Storage and Handling

Labeled, packaged study drugs will be shipped to each site by the Sponsor or designee following receipt of the necessary regulatory documents. The Investigator or an approved representative (e.g., registered pharmacist) will ensure that all study drugs are stored as outlined in the Investigational Product (IP) Manual and in accordance with applicable regulatory requirements. The drug storage area at the site must be secure, with access limited to authorized personnel.

Stability studies to support drug storage conditions for encorafenib and binimetinib have been conducted by the Sponsor or an affiliate. The Sponsor will continue to monitor the stability of encorafenib and binimetinib and will alert the site if a lot is nearing the end of its anticipated shelf life.

Detailed instructions for storage and handling of study drugs will be provided in the IP Manual.

6.3.3. Accountability and Return of Study Drug Supply

The Investigator or an approved representative (e.g., pharmacist) must maintain accurate records of dates and quantities of study drug received, to whom study drug is dispensed (patient-by-patient accounting), and accounts of any study drug accidentally or deliberately destroyed. The Investigator must retain all unused or expired study drug supplies until the study monitor has confirmed the accountability data. If a site's policy prohibits holding study drug supplies for monitor review, then a copy of the standard operating procedure (SOP) for processing drug returns must be provided to the Sponsor.

To ensure adequate records, all study drug will be accounted for on a drug accountability inventory form as instructed by the Sponsor. Refer to the IP Manual for details on how to process all unused or expired study supplies.

6.4. Study Drug Dispensing and Administration

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drugs will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Patients will receive a diary to document self-administered dosing of study drugs to include the dose of study drugs taken, the date of dosing (and times if applicable), and if any doses were missed and the reason for the missed dose. Diaries will be provided on a regular basis. Patients will be instructed to return unused study drugs and the patient diary to the site at each visit.

Patients should not take extra doses of study drugs to compensate for doses missed for AEs or any other reason. If a patient vomits at any time after dosing, the dose of study drugs should not be re-administered.

The pharmacist or study nurse will ensure that the appropriate dose is dispensed and will provide the patient with at least the appropriate number of tablets for the number of doses to be taken prior to the next scheduled visit. The site personnel will train the patient and/or the patient's caregiver on dosing procedures for the study drugs.

Agents comprising the CYP probe cocktail and rosuvastatin will be centrally provided, based on local regulations and requirements. Complete dispensing instructions, dosing instructions (including the timing of administration), will be provided in the Pharmacy Manual.

6.5. Dose Modifications and Reductions

For patients who do not tolerate encorafenib and/or binimetinib initial dosing schedule, dose adjustment is permitted in order to allow the patient to continue on study drug (see Table 3 for encorafenib and Table 4 for binimetinib). If patients require a dose reduction, in particular for encorafenib, during the DDI phase, the patient may be replaced (see Section 9.2).

A dose reduction below 75 mg QD for encorafenib and below 15 mg BID for binimetinib is not allowed. If a patient misses 3 or more consecutive doses of encorafenib and binimetinib in any arm or 3 or more doses of modafinil in Arm 3 during the DDI phase due to noncompliance, the patient may remain on treatment but may be replaced if limited data are available from the patient. Dose interruptions of more than 28 consecutive days in the post-DDI phase are not allowed unless approved by the study Medical Monitor.

Table 3. Dose Reduction for Encorafenib

Dose Level	Encorafenib Dose and Schedule
0	450 mg QD
-1	300 mg QD
-2	225 mg QD
-3	150 mg QD
-4	75 mg QD[a]

Abbreviation: QD = once daily
a Dose reduction below 75 mg is not allowed

Table 4. Dose Reduction for Binimetinib

Dose Level	Binimetinib Dose and Schedule
0	45 mg BID
-1	30 mg BID
-2	15 mg BID[a]

Abbreviation: BID = twice daily
a Dose reduction below 15 mg is not allowed

Doses of encorafenib that are omitted for AEs or any other reason can be taken up to 12 hours prior to the next dose. Doses of binimetinib that are omitted for AEs or any other reason should not be made up. For both encorafenib and binimetinib, when the toxicity that resulted in a dose reduction improves to Grade 1 or less, the dose should be re-escalated at the Investigator's discretion provided there are no other concomitant toxicities.

If encorafenib is dose reduced due to prolonged QTcF > 500 msec, no dose re-escalation is allowed. If binimetinib is dose reduced due to left ventricular dysfunction, no dose re-escalation is allowed. Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below (Table 5). In general, doses should not be reduced or interrupted for Grade 1 toxicities, but treatment to control symptoms should be provided as appropriate. All AEs should be followed weekly or as clinically appropriate until stabilization or resolution.

If a patient discontinues treatment with binimetinib, the patient may continue treatment with encorafenib at the R2PD single-agent dose of 300 mg QD. However, due to the limited efficacy of binimetinib alone in the study population, if a patient discontinues treatment with encorafenib, they must discontinue treatment with binimetinib and complete the Day 30 Safety Follow-up Visit.

Please refer to Table 5 for dose adjustment recommendations for encorafenib and/or binimetinib induced toxicities. Please refer to Appendix 2 for additional supportive care guidelines for the management of encorafenib induced HFSR. Furthermore, please refer to

Appendix 1 and Appendix 3 for additional supportive care guidelines for the management of encorafenib and binimetinib induced skin toxicity and diarrhea respectively.

Please see Appendix 13 for alternative study measures to be followed during public emergencies, including the COVID-19 pandemic.

Table 5. Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	**Dose Modification for Encorafenib and for Binimetinib**
Eye Disorders - Retinal Events (including serous detachment of the retina) **Note: Results and images of ocular coherence tomography (OCT) must be made available upon request.** **Any visual acuity impairment at screening should be documented and should be considered as baseline.**	
Grade 1	Maintain dose levels of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days • If patient remains asymptomatic (Grade 1), maintain dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If patient becomes symptomatic (blurred vision, photophobia, etc.) or visual acuity assessment shows Grade 2, follow Grade 2 dose guidelines below
Grade 2	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days • If resolved to baseline or Grade ≤ 1, resume treatment at current dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If not resolved to baseline or Grade ≤ 1, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If posterior uveitis lasts > 6 weeks, permanently discontinue binimetinib and encorafenib.
Grade 3	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days: • If posterior uveitis resolves to baseline or Grade ≤ 1 in < 6 weeks, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If posterior uveitis does not resolve to baseline or Grade ≤ 1 in < 6 weeks, permanently discontinue binimetinib and encorafenib • If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If not resolved to baseline or Grade ≤ 2, continue the interruption and repeat the ophthalmic assessment in 10 days.

Table 5. Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	**Dose Modification for Encorafenib and for Binimetinib**
	○ If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol ○ If remains Grade 3, permanently discontinue encorafenib and binimetinib
Grade 4	Permanently discontinue encorafenib and binimetinib and immediately follow-up with ophthalmic monitoring[c]
Eye Disorders - Posterior Uveitis[c] **Note: Results and images of ocular coherence tomography (OCT) must be made available upon request.** **Any visual acuity impairment at screening should be documented and should be considered as baseline.**	
Grade 1	Maintain dose levels of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days. • If subject remains asymptomatic (Grade 1), maintain dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol. If subject becomes symptomatic (blurred vision, photophobia, etc.) or visual acuity assessment shows Grade 2, follow Grade 2 dose guidelines below.
Grade 2	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days. • If resolved to baseline or Grade ≤ 1, resume treatment at current dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol. • If not resolved to baseline or Grade ≤ 1, resume treatment at 1 reduced dose level[b] of encorafenib and current dose of binimetinib and continue the schedule of visual assessments established per protocol. If posterior uveitis lasts > 6 weeks, permanently discontinue binimetinib and encorafenib.
Grade 3	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days: • If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose level[b] of encorafenib and current dose of binimetinib and continue the schedule of visual assessments established per protocol. • If not resolved to baseline or Grade ≤ 2, continue the interruption and repeat the ophthalmic assessment in 10 days. If remains Grade 3, permanently discontinue encorafenib and binimetinib.
Grade 4	Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring[c].
Eye Disorder - RVO[c]	

Table 5. Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	**Dose Modification for Encorafenib and for Binimetinib**
Note: Results and images of ophthalmic examinations should be made available upon request. This includes scans/images of fluorescein angiography should a patient be assessed using this technique.	
RVO of any grade	Permanently discontinue encorafenib and binimetinib and immediately follow-up with ophthalmic monitoring[c]
Other Eye Disorders (i.e., Non-retinal and Non-uveitis Events)	
Grade 1 – 2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution
Grade 3	Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days[c]: • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution[c]
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution[c]
Liver-related Adverse Events	
Grade 1 AST or ALT > ULN to 3 × ULN	Maintain dose level of encorafenib and binimetinib
Grade 2 AST or ALT > 3 to 5.0 × ULN or 3 × baseline value[d] **AND** **blood bilirubin[g] ≤ 2.0 × ULN**	Maintain dose level of encorafenib and interrupt dosing of binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, maintain dose level of encorafenib and binimetinib • If not resolved in ≤ 14 days, interrupt dose of encorafenib (in addition to prior binimetinib) until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at current dose level of encorafenib and 1 reduced dose level[b] of binimetinib If additional occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib Treatment with encorafenib and binimetinib may be resumed sequentially at the Investigator's discretion, with encorafenib being resumed alone for one week before resuming binimetinib treatment
AST or ALT > 3.0 to 5.0 × ULN **AND** **blood bilirubin[g] > 2.0 × ULN**	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1, then: • If resolved in ≤ 7 days, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib • If not resolved in ≤ 7 days, permanently discontinue encorafenib and binimetinib

Table 5. Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	**Dose Modification for Encorafenib and for Binimetinib**
	Treatment with encorafenib and binimetinib may be resumed sequentially at the Investigator's discretion, with encorafenib being resumed alone for one week before resuming binimetinib treatment
Grade 3 AST or ALT > 5.0 to 8.0 × ULN) **AND blood bilirubin[g] ≤ 2.0 × ULN**	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, resume treatment at current dose level of encorafenib and binimetinib • If not resolved in ≤ 14 days, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib Treatment with encorafenib and binimetinib may be resumed sequentially at the Investigator's discretion, with encorafenib being resumed alone for one week before resuming binimetinib treatment If additional occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib
AST or ALT >8 × ULN **AND blood bilirubin[g] ≤ 2.0 × ULN**	Permanently discontinue encorafenib and binimetinib
AST or ALT > 5.0 × ULN **AND blood bilirubin[g] > 2.0 × ULN**	Permanently discontinue encorafenib and binimetinib
Grade 4 AST or ALT > 20.0 × ULN	Permanently discontinue encorafenib and binimetinib
Cardiac Disorders - Left Ventricular Systolic Dysfunction[a] (Dose Adjustment for Binimetinib ONLY)	
Asymptomatic absolute decrease of > 10% in LVEF compared to baseline and the LVEF is below the institution's lower limit of normal (LLN) (e.g., a decrease of 60% to 48% is an absolute decrease of 12%)	Interrupt dosing of binimetinib and repeat evaluation of LVEF within 2 weeks • If the LVEF recovers (defined as LVEF ≥ 50% or ≥ LLN and absolute decrease ≤ 10% compared to baseline) ≤ 21 days, resume treatment at 1 reduced dose level[b] of binimetinib after approval of the Sponsor Medical Monitor. Monitor LVEF 2 weeks after resuming binimetinib, every 4 weeks for 12 weeks and subsequently as per protocol • If the LVEF does not recover in ≤ 21 days, permanently discontinue binimetinib. Closely monitor LVEF until resolution or for up to 16 weeks

Table 5. Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	**Dose Modification for Encorafenib and for Binimetinib**
Grade 3 – 4	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks Note: Copies of ECHO and/or MUGA scans could be requested for patients to be available to the Sponsor for patients with absolute decrease of >10% in LVEF compared to baseline and LVEF < 50% or LLN
CK Elevation	
Grade 1-2	Maintain dose of encorafenib and binimetinib. Ensure patient is adequately hydrated. Closely monitor CK and serum creatinine • If total CK ≥ 3 × ULN, measure CK isoenzymes and myoglobin in blood or urine
Grade 3 > 5.0 - 10.0 x ULN **without** renal impairment (i.e., serum creatinine < 1.5 × ULN or 1.5 × baseline)	If asymptomatic, maintain dosing of encorafenib and binimetinib. Ensure patient is adequately hydrated. Monitor and measure isoenzymes and myoglobin in blood or urine and serum creatinine If symptomatic (muscle pain/spasms/muscle weakness), maintain dosing of encorafenib and interrupt dosing of binimetinib until resolved to CTCAE Grade ≤ 1 and monitor closely, then: • If resolved in ≤ 21 days, maintain dose of encorafenib and resume treatment at 1 reduced dose level[b] of binimetinib • If not resolved in ≤ 21 days, maintain dose of encorafenib and permanently discontinue binimetinib
Grade 4 **without** renal impairment (i.e., serum creatinine < 1.5 × ULN or 1.5 × baseline)	If asymptomatic, maintain dose of encorafenib and interrupt dosing of binimetinib. Ensure patient is adequately hydrated. Monitor and measure isoenzymes and myoglobin in blood or urine and serum creatinine • If resolved in ≤ 21 days, maintain dose of encorafenib and resume treatment at 1 reduced dose level[b] of binimetinib • If not resolved in ≤ 21 days, maintain dose of encorafenib and permanently discontinue binimetinib If symptomatic (muscle pain/spasms/muscle weakness), maintain dose of encorafenib and permanently discontinue binimetinib
Grade 3 or 4 **with** renal impairment (i.e., serum creatinine ≥ 1.5 × ULN or 1.5 × baseline)	Interrupt dosing of encorafenib and binimetinib until resolved to CTCAE Grade < 1 or baseline level. Ensure patient is adequately hydrated. Monitor closely and measure isoenzymes and myoglobin in blood or urine and serum creatinine, then: • If resolved in ≤ 21 days, consider resuming treatment at 1 reduced dose level[b] of encorafenib and binimetinib • If not resolved in ≤ 21 days, permanently discontinue encorafenib and binimetinib 2nd occurrence: • Permanently discontinue encorafenib and binimetinib
Cardiac Investigation – Prolongation of the QT Interval QTcF Value	

Table 5. Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	**Dose Modification for Encorafenib and for Binimetinib**
QTcF > 500 ms during treatment and change from pre-treatment value remains ≤ 60 ms	Electrolyte abnormalities, including magnesium, should be corrected and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. 1st occurrence: • Temporarily interrupt dosing of encorafenib until QTcF < 500 ms. Then resume treatment at 1 reduced dose level[b] of encorafenib 2nd occurrence: • Temporarily interrupt dosing of encorafenib treatment until QTcF < 500 ms. Then resume treatment at 1 reduced dose level[b] of encorafenib 3rd occurrence: • Permanently discontinue encorafenib and binimetinib
QTcF increase during treatment is both > 500 ms and > 60 ms change from pre-treatment values	Electrolyte abnormalities, including magnesium, should be corrected and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. Permanently discontinue encorafenib and binimetinib
Rash (see Appendix 1)	
Grade 1	Maintain dose level of encorafenib and binimetinib Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored
Grade 2	1st occurrence: • Maintain dose level of encorafenib and binimetinib • Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib and binimetinib. For dermatitis acneiform, treatment with encorafenib may be maintained if, in the judgment of the Investigator, the rash is considered to be unrelated to encorafenib. If treatment with encorafenib was maintained and no improvement within 8 days, interrupt dosing of encorafenib 2nd occurrence: • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib and 1 reduced dose level[b] of binimetinib. For dermatitis acneiform rash, treatment with encorafenib may be maintained if, in the judgment of the Investigator, the rash is considered to be unrelated to encorafenib. If treatment with encorafenib was maintained and no improvement within 8 days, interrupt dosing of encorafenib

Table 5. Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	**Dose Modification for Encorafenib and for Binimetinib**
Grade 3	1st occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Reassess weekly. Then resume treatment at current dose level of encorafenib and binimetinib. • Consider referral to dermatologist and manage rash per dermatologist's recommendation. 2nd occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib. Resume treatment with encorafenib at the same dose level if, in the judgment of the Investigator, the rash is considered to be unrelated to encorafenib • Consider referral to dermatologist and manage rash per dermatologist's recommendation
Grade 4	Permanently discontinue encorafenib and binimetinib[f]
Hand-foot Skin Reaction (HFSR)/Palmar-plantar Erythrodysesthesia Syndrome[e] (Dose Adjustment for Encorafenib ONLY) (see Appendix 2)	
Grade 1	Maintain dose of encorafenib. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications.
Grade 2	1st occurrence: • Maintain dose of encorafenib and HFSR should be closely monitored. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. • If no improvement ≤ 14 days, interrupt dosing of encorafenib until resolved to Grade ≤ 1. Resume treatment with encorafenib at current dose level. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Additional occurrence: • Treatment with encorafenib may be maintained or interrupted based upon the Investigator's discretion. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. • If interrupted dosing of encorafenib per Investigator's judgment, interrupt until resolved to Grade ≤ 1. Resume treatment with encorafenib at the same dose level or 1 reduced dose level[b] based upon the Investigator's discretion.
Grade 3	1st or additional occurrence: • Interrupt dosing of encorafenib until resolved to Grade ≤ 1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Reassess the patient weekly. Then resume treatment at one reduced dose level[b] of encorafenib • Consider referral to dermatologist and manage HFSR per dermatologist's recommendation > 3nd occurrence:

Table 5. Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	**Dose Modification for Encorafenib and for Binimetinib**
	• Interrupt dosing of encorafenib until resolved to Grade ≤ 1, decision to resume treatment with encorafenib at one reduced dose level[b] or permanently discontinue encorafenib should be based upon the Investigator's discretion.
Squamous Cell Carcinoma (SCC), Keratoacanthoma (KA) and any Other Suspicious Skin Lesion (Dose Adjustment for Encorafenib ONLY)	
Grade ≤ 3	Maintain dose of encorafenib (dose interruptions or modifications are not required). Treatment of SCC, KA, and any other suspicious skin lesion (eg. new primary melanoma) should occur based upon institutional practice.
Diarrhea (see Appendix 3)	
Uncomplicated Grade 1-2	Maintain dose of encorafenib. Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of binimetinib
Complicated Grade 1-2	Consider temporary interruption of encorafenib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib Interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level[b] of binimetinib
Grade 3-4	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib if, in the judgment of the Investigator, the toxicity is considered to be unrelated to encorafenib, or at one reduced dose level[b]. Resume treatment at 1 reduced dose level of binimetinib
Nausea/Vomiting	
Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level[b] of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level[b]. Note: Interrupt dosing of encorafenib and binimetinib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice)
Grade 4	Permanently discontinue encorafenib and binimetinib[f]
Interstitial Lung Disease/Pneumonitis (see Appendix 4)	
Grade 1	Maintain dose level of encorafenib and binimetinib.
Grade 2	Maintain dose of encorafenib. Withhold binimetinib for up to 3 weeks. If improved to Grade 0 or 1, resume treatment at 1 reduced dose level of binimetinib. If not resolved within 3 weeks, permanently discontinue binimetinib.
Grade 3-4	Permanently discontinue binimetinib.
All Other Adverse Events (Suspected To Be Related To Encorafenib and/or Binimetinib)	
Grade 1-2	If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider interruption or reduction of encorafenib and binimetinib, as applicable

Table 5. Encorafenib and Binimetinib – Recommended Dose Modifications Associated with Treatment-Related Adverse Events

Worst toxicity CTCAE, v.4.03 Grade (unless otherwise specified[a])	Dose Modification for Encorafenib and for Binimetinib
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤1 or to pretreatment/baseline level. If the event resolves ≤ 21 days, then study drug may be resumed at 1 reduced dose level[b] based upon the Investigator's discretion.
Grade 4	Permanently discontinue encorafenib and binimetinib[f]

a Not according to NCI CTCAE
b Dose reduction below 75 mg QD for encorafenib, and below 15 mg BID for binimetinib is not allowed.
c Ophthalmic monitoring mandated for retinal events, posterior uveitis, RVO: further evaluation with specialized retinal imaging (e.g. ocular coherence tomography, fluorescein angiography). Any diagnosis of retinal events must be supported by presence or absence of symptoms, visual acuity assessment and findings in OCT.
d For patients enrolled with liver metastases and baseline LFT elevations.
e Disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.
f A patient with a Grade 4 AE may resume treatment at the lower dose level if the AE recovers to Grade ≤ 1 within 28 days of discontinuing drug in the post-DDI phase and, if in the opinion of the Investigator and Sponsor Medical Monitor, the event is not life-threatening and the patient can be managed and monitored for recurrence of AE. Any patients requiring a treatment interruption of duration > 28 days must discontinue study drug permanently.
g Refers to total bilirubin.

6.5.1. Follow-up for Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts such as an ophthalmologist, cardiologist or dermatologist should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study drug induced toxicities are provided in Table 5. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.5.1.1. Management of Hand Foot Skin Reaction (HFSR)

Because HFSR has been reported for encorafenib, it is recommended that patients are educated prior to starting study treatment to avoid activities that can cause friction on hands and feet. In addition, supportive measures for prevention and/or management of HFSR should be instituted. Clinical judgment and experience of the treating physician should guide the management plan of each patient.

Dose reduction/interruption/discontinuation decisions for HFSR should be based on the CTCAE grade of the toxicity and the guidelines provided in Table 5.

Additional recommended guidance is provided for the prevention, management and support of HFSR in Appendix 2. A visit at a podiatrist may also be recommended at the discretion of the Investigator.

6.5.1.2. Follow-up Evaluations for Appearance of Keratoacanthoma (KA) and/or Squamous Cell Carcinoma (SCC)

The skin of patients should be examined regularly to monitor for the possible development of KA and/or SCC, as these have been reported to occur under selective BRAF inhibitor treatment (Flaherty et al 2010; Kefford et al 2010; Robert et al 2011). Patients should be instructed to inform their physicians upon the occurrence of any skin changes. In case of occurrence of KA and/or SCC, patients' treatment will follow institutional standards. Results of biopsies will be collected. A dermatological exam is recommended to be performed every 8 weeks for up to 6 months following discontinuation of encorafenib.

6.5.1.3. Management of Nausea and/or Vomiting

Because nausea and vomiting have been reported for encorafenib and binimetinib, it is recommended that patients are educated on the possibility of occurrence of these side effects prior to starting study treatment. Patient education as well as proper management of nausea and/or vomiting at the first sign is important. Ondansetron is recommended for management during the DDI phase, however, clinical judgment and experience of the treating physician should guide the management plan of each patient.

In the post-DDI phase, patients experiencing nausea and/or vomiting CTCAE ≥ 1 may receive antiemetics at the discretion of the treating physician (as per local guideline). It is recommended that patients be provided a prescription for antiemetics, and are instructed on the use of antiemetics on the first day of study drug treatment. Prophylactic antiemetics such as dexamethasone 8 mg, prochlorperazine, or metoclopramide may be administered to patients on an "as needed" basis.

Dose interruption/reduction decisions for nausea and/or vomiting should be based on the CTCAE grade of the toxicity and the guidelines provided in Table 5.

As a guidance for recommendations on supportive measures for the prevention and/or management of nausea and/or vomiting, the published recommendation from American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and Multinational Association of Supportive Care (MASCC) can be used (Basch et al 2011; Roila et al 2010).

6.6. Treatment Compliance

Compliance will be evaluated at each visit by a review of patient diary entries, an accounting of returned drug product, and patient interviews during the DDI Phase of the study.

7. STUDY PROCEDURES AND ASSESSMENTS

The procedures and assessments that will be conducted during this study are described in this section in narrative form, described by study visit in Section 8 and summarized in Table 7 and Table 8.

Written informed consent must be granted by each patient prior to the initiation of any study procedure or assessment (other than those considered standard of care).

Please see Appendix 13 for alternative study measures to be followed during public emergencies, including the COVID-19 pandemic.

7.1. Safety Assessments

7.1.1. Adverse Events

Adverse events will be assessed by direct observation and patient interviews. Patients should be questioned using non-leading questions. Assessment and reporting of AEs is described in detail in Section 10.

7.1.2. Medical History

Significant (at the Investigator's discretion) past and present medical history will be recorded. Medical history will include alcohol and nicotine use for the 3 months before screening. Any ongoing condition observed prior to the initiation of study treatment will be recorded.

7.1.3. Physical Examination

Full physical examinations will be performed by trained medical personnel at the time points specified in Table 7 and Table 8.

Vital signs (blood pressure, pulse and temperature) will be measured per institutional standards as part of the physical examination. Height will be measured only at screening. All physical examinations occurring on dosing days must be performed prior to study drug administration. Significant findings in the Investigator's opinion that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant findings made after signing the study informed consent which meet the definition of an AE must be recorded on the Adverse Event eCRF.

7.1.4. Electrocardiogram

Triplicate 12-lead ECGs will be performed at the time points specified in Table 7 and Table 8. At each measurement, 3 serial ECGs will be obtained within approximately 5 to 10 minutes total time. Triplicate 12-lead ECGs will be performed at predose (up to 30 minutes before any study drug administration) and for all protocol specified post-baseline assessments. Postdose ECGs are to be performed at all protocol specified post-baseline assessments (± 30 minutes). Triplicate 12-lead ECGs are to be performed during the post-DDI phase if clinically indicated.

The mean of the triplicate ECG measurements performed at baseline will serve as each patient's baseline value for all postdose comparisons. When ECGs and PK sampling are performed at the same nominal time point, the ECGs will be performed first.

An abnormal ECG (e.g., QTc of > 500 ms or with a change in QTc from baseline of ≥ 60 ms) may be repeated if it cannot be interpreted by the Investigator. ECG tracings should be made available if requested by the Sponsor for central assessment by an independent reviewer.

QT interval values will be corrected for heart rate using the Fridericia formula (QTcF).

7.1.5. ECOG Performance Status

Assessment of ECOG PS will be conducted at the time points specified in Table 7 and Table 8.

7.1.6. Clinical Laboratory Tests

Blood and urine samples for the laboratory tests listed in Table 6 will be collected as outlined in Section 8 and at the time points specified in Table 7 and Table 8.

Table 6. Summary of Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Coagulation	Others
Hemoglobin Hematocrit RBC Platelets WBC Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Albumin Alkaline phosphatase ALT Amylase AST Bicarbonate (CO_2) Total bilirubin Direct bilirubin (if total bilirubin values are abnormal) BUN Calcium Chloride CK (If total CK ≥3 X ULN, then measure isoenzymes, serum creatinine and myoglobin in blood or urine weekly.) Creatinine Glucose LDH Lipase Magnesium Inorganic phosphate Potassium Total protein Sodium Uric acid	Appearance Color Specific gravity pH Protein Glucose Ketones Blood Nitrite Leukocyte esterase If urinalysis is abnormal, then microscopy: • WBC • RBC • Bacteria • Epithelial cells • Casts	PT or INR aPTT	At screening only: • Hepatitis B surface antigen • Hepatitis B surface antigen antibody • Hepatitis C core antibody • HIV, as applicable per local regulations • Urine cotinine test (Arm 1 only) If applicable: • Serum pregnancy test • Urine pregnancy test • FSH • Urine drug and alcohol testing

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; RBC = red blood cells; WBC = white blood cells

7.1.6.1. Hematology, Clinical Chemistry and Urinalysis

Site-specific handling instructions for hematology, clinical chemistry and urinalysis samples should be followed. Screening results will be assessed by the Investigator to determine patient eligibility. Day -7 (Arms 1 and 2) and Day 1 (Arm 3) results will be assessed by the Investigator prior to first dose of study treatment. Additional clinical laboratory tests may be obtained at any time during the study at the Investigator's discretion. Clinically significant findings should be followed to resolution or stabilization.

Blood and urine sample collections on clinic days must be performed prior to study treatment administration. Laboratory test results required to make decisions regarding potential dose modifications during the post-DDI phase (as specified in Section 6.5) should be reviewed prior to study treatment administration.

7.1.7. Ophthalmic Examination

7.1.7.1. Routine Testing

Full ophthalmic examination including slit lamp examination, best recorded visual acuity for distance testing, intraocular pressure (IOP) and dilated funduscopy with attention to retinal abnormalities, especially retinal pigment epithelial detachment (RPED), retinal detachment (serous or rhegmatogenous), and retinal vein occlusion (RVO), will be performed at the time points listed in Table 7 and Table 8 during on-study treatment phase and at EOT. Ophthalmic examinations are to be performed during the post-DDI phase if clinically indicated.

7.1.7.2. Additional testing

Patients with clinical suspicion of retinal abnormalities (i.e. photopsia, metamorphopsia, impairment of visual acuity, etc.) RVO, **must** complete at least one of the following additional assessments**:**

- For retinal abnormalities: optical coherence tomography of the macula (spectral domain is preferred)
- For vascular abnormalities: fluorescein angiography of the central 30 degrees.

Any diagnosis of a retinal event (e.g.: macular edema, detachment) should have its evolution/resolution substantiated by OCT.

Images of the ophthalmic exams, especially OCT and/or fluorescein angiography should be sent to the investigative site along with the results of the exam and be maintained in the patient's source document file. These images may be requested to be sent to the Sponsor or designee.

7.1.8. Dermatologic Examination

The possible appearance of SCC, KA or other suspicious skin lesion will be monitored. Dermatologic evaluations will be performed as a part of the physical examinations at the timepoints specified Table 7 and Table 8. Patients should be instructed to inform their physician upon the occurrence of any skin changes. Dermatologist examination and/or dermatologic biopsy will be performed only if clinically indicated. In the occurrence of these lesions, the lesions should be removed and the patient must be treated as per institutional practice. Biopsy results will be collected.

7.1.9. Pregnancy Tests

All females of childbearing potential are required to undergo serum pregnancy assessments at screening and serum or urine pregnancy assessments during the study at the time points specified in Table 7 and Table 8. Any positive test will result in immediate cessation of study drug administration.

Urine pregnancy tests will be performed locally as outlined in the SoA, as medically indicated (e.g., in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). All blood and urine collections for pregnancy tests occurring on dosing days must be performed prior to study drug administration, with a negative test result required prior to administration of study treatment.

If a urine pregnancy test is positive, the results will be confirmed with a serum pregnancy test. If the serum pregnancy test is negative after a urine test was positive, the Investigator will assess the potential benefit/risk to the patient and determine whether it is in the patient's best interest to resume study treatment and continue participation in the study. Any female patient who becomes pregnant while participating in the study will be instructed to immediately discontinue study treatment. If pregnancy is confirmed by a serum pregnancy test, see Section 10 for reporting requirements.

Females of nonchildbearing potential do not require pregnancy tests. This includes women who have undergone hysterectomy, bilateral oophorectomy, bilateral tubal ligation or who are over the age of 55 and amenorrheic. Women of age 55 and under and who are amenorrheic should have FSH measurement within the postmenopausal range for the institution to be considered of nonchildbearing potential.

All blood and urine collections for pregnancy tests occurring on dosing days must be performed prior to study drug administration.

7.2. Pharmacokinetic Assessments

A 6-mL venous blood sample (Arms 1 and 2) or a 4-mL venous blood sample (Arm 3) for measurement of plasma concentrations of encorafenib (and its metabolite, LHY746), binimetinib (and its metabolite, AR00426032), midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxy omeprazole, rosuvastatin, bupropion and/or hydroxybupropion will be drawn at each time point specified in Table 7 and Table 8. Analytes for quantitation will depend on the study arm. Complete instructions for sample collection, processing, handling and shipment will be provided in the Laboratory Manual.

All PK samples up to and including the 8-hour time point must be obtained within 15 minutes of the designated collection time. Predose PK samples must be obtained prior to, but within 30 minutes of, administration of any study drug or probe substrate.

All urine during the 0 to 8 hour interval is to be collected from patients in Arm 1 for measurement of urine concentrations of losartan, E-3174, dextromethorphan and dextrorphan. Patients should attempt to void as close to the 8 hour time point as possible. The urine from timepoints 0 hour through 8 hours will be pooled and refrigerated during the collection interval.

At the end of each interval, total urine volume will be measured using a cylindrical graduate and recorded.

Refer to the Laboratory Manual for further details regarding urine sample processing.

If vomiting occurs within 4 hours following study drug administration on the day of PK blood sampling, the time (using the 24-hour clock) of vomiting should be recorded on the transmittal forms that accompany the sample and that dose of study drug should not be re-administered.

During the COVID-19 pandemic, please proactively discuss any PK collection issue with the Pfizer clinician and clinical pharmacologist.

CCI [redacted]

7.4. Disease Assessments

Tumor assessments will include imaging (e.g., CT, MRI) and caliper measurements, as applicable, and will be performed at screening. Tumor response will be evaluated locally by the Investigator according to RECIST, v1.1 (Appendix 7).

Although this study does not formally assess efficacy, efficacy assessment are required every 8-12 weeks in order for the Investigator to assess continued benefit.

8. SCHEDULE OF PROCEDURES AND ASSESSMENTS

Before recruitment of patients into the study, written ethic committee (EC) approval of the protocol, informed consent, and any additional patient information must be obtained.

During screening, a unique number will be assigned to each patient who provides written informed consent. Once a patient is in screening or is enrolled in the study, that patient will be identified only by the assigned patient number.

The Investigator or designee is responsible for verifying that the patient is eligible before enrolling the patient.

At the site, the Investigator will maintain a log for all screened patients (including patients who fail screening after providing written informed consent) and all enrolled patients.

Please see Appendix 13 for alternative study measures to be followed during public emergencies, including the COVID-19 pandemic.

The procedures and assessments that will be conducted during this study are described in this section by study visit and summarized in Table 7 and Table 8.

8.1. Prescreening Evaluations

Prescreening evaluations must be performed between Day -57 and Day -36 in Arms 1 and 2 and between Day -50 and Day -29 in Arm 3. These include:

- Mutation prescreen consent
- Tumor sample

8.2. Screening Evaluations

All screening procedures must be performed within 28 days prior to the first dose of study drug on Day -7 (Day -35 to Day -8, inclusive) in Arms 1 and 2 and prior to the first study drug dose on Day 1 (Day -28 to Day -1, inclusive) in Arm 3. These include:

- Confirm *BRAF* mutation status
- Administration of written informed consent (**must be obtained prior to performance of any study-specific tests or evaluations that are not considered standard of care**)
- Disease assessments based on RECIST v1.1 (imaging and /or caliper measurements; can be up to Day -49 but must be confirmed by Day -7; if a patient has had an imaging assessment up to 6 weeks prior to Day -7 [Day -49 to Day -7], repeat assessment is not required)
- Demographics
- Medical history, including alcohol and nicotine use for the 3 months before screening

- Verification of eligibility criteria
- Prior treatments, including all cancer treatments, and any other prior treatments (i.e., other than cancer treatments) taken within 4 weeks before screening
- ECOG PS
- Full physical exam, including body weight and height
- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time
- ECHO/MUGA
- Ophthalmic examination
- Blood samples for the following tests:
    - Serum pregnancy test (females of childbearing potential only)
    - Serum FSH, as applicable to confirm menopausal status
    - Clinical chemistry, coagulation and hematology
    - CCI [redacted]
- Urine sample for the following tests:
    - Urinalysis
    - Urine cotinine (Arm 1 only)
- Review of concomitant medications
- Review of AEs

8.3. Study Evaluations

8.3.1. DDI Phase – Arms 1 and 2

8.3.1.1. Day -7 at Hour 0

- Verification of eligibility criteria
- Weight
- Vital signs, including blood pressure, pulse, and temperature

- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time (repeat if QTcF > 480 msec)
- Blood samples for the following tests:
    - Pharmacokinetics
    - Clinical chemistry, coagulation and hematology
    - Serum (or urine) pregnancy test (females of childbearing potential only)
- Urine sample for the following tests:
    - Pharmacokinetics – Arm 1 only (pre-dose sample will not be pooled with subsequent post-dose samples)
    - Urinalysis
    - Urine (or serum) pregnancy test (females of childbearing potential only)
    - Drug and alcohol testing
- Review of concomitant medications
- Review of AEs
- Administration/dispensing of CYP probe cocktail (Arm 1 only)
- Administration/dispensing of rosuvastatin (Arm 2 only)

8.3.1.2. Day -7 at Hours 1 and 3

- Urine sample for PK – Arm 1 only (sample to be included in a pooled urine sample of all urine collected from time 0 [postdose] to 8 hours post-dose)
- Blood sample for PK
- Review of AEs

8.3.1.3. Day -7 at Hours 2, 4, 6 and 8

- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time
- Urine sample for PK – Arm 1 only (sample to be included in a pooled urine sample of all urine collected from time 0 [postdose] to 8 hours post-dose)
- Blood sample for PK

- Review of AEs

8.3.1.4. Day 1 and Day 14 at Hour 0

- Weight
- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time
- Blood samples for the following tests:
    - Pharmacokinetics
    - Clinical chemistry, coagulation and hematology
    - Serum (or urine) pregnancy test (females of childbearing potential only)
- Urine samples for the following:
    - Pharmacokinetics – Arm 1 only (pre-dose sample will not be pooled with subsequent post-dose samples)
    - Urinalysis
    - Urine (or serum) pregnancy test (females of childbearing potential only)
- Review of concomitant medications
- Review of AEs
- Administration/dispensing of encorafenib and binimetinib
- Administration/dispensing of CYP probe cocktail (Arm 1 only)
- Administration/dispensing of rosuvastatin and bupropion (Arm 2 only)
- Assess compliance with administration of encorafenib and binimetinib on Day 14

8.3.1.5. Day 1 and Day 14 at Hours 1 and 3

- Urine sample for PK – Arm 1 only (sample to be included in a pooled urine sample of all urine collected from time 0 [postdose] to 8 hours postdose)
- Blood sample for PK
- Review of AEs

8.3.1.6. Day 1 and Day 14 at Hours 2, 4, 6 and 8

- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time
- Urine sample for PK – Arm 1 only (sample to be included in a pooled urine sample of all urine collected from time 0 [postdose] to 8 hours postdose)
- Blood sample for PK
- Review of AEs

8.3.2. DDI Phase – Arm 3

8.3.2.1. Day 1 and 15 at Hour 0

- Verification of eligibility criteria (Day 1 only)
- Weight (Day 1 only)
- Blood samples for the following tests (Day 1 only):
    - Clinical chemistry, coagulation and hematology
    - Serum (or urine) pregnancy test (females of childbearing potential only)
- Urine sample for the following tests (Day 1 only):
    - Urinalysis
    - Urine (or serum) pregnancy test (females of childbearing potential only)
    - Drug and alcohol testing
- Review of concomitant medications (Day 1 only)
- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time (repeat if QTcF > 480 msec)
- Review of AEs
- Administration/dispensing of encorafenib and binimetinib
- Administration/dispensing of modafinil (Day 15 only)

8.3.2.2. Day 1 and 15 at Hours 2 and 4

- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time
- Review of AEs

8.3.2.3. Day 14 and 21 at Hour 0

- Weight
- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time
- Blood samples for the following tests:
    - Pharmacokinetics
    - Clinical chemistry, coagulation and hematology
    - Serum (or urine) pregnancy test (females of childbearing potential only)
- Urine samples for the following:
    - Urinalysis
    - Urine (or serum) pregnancy test (females of childbearing potential only)
- Review of concomitant medications
- Review of AEs
- Administration/dispensing of encorafenib and binimetinib
- Administration of modafinil (Day 21 only)
- Assess compliance with administration of modafinil, encorafenib and binimetinib

8.3.2.4. Day 14 and Day 21 at Hours 1 and 3

- Blood sample for PK
- Review of AEs

8.3.2.5. Day 14 and Day 21 at Hours 2, 4, 6 and 8

- Vital signs, including blood pressure, pulse, and temperature

- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time
- Blood sample for PK
- Review of AEs

8.3.3. Day 28, End of DDI Phase Visit

- Full physical exam, including body weight
- Vital signs, including blood pressure, pulse, and temperature
- Triplicate 12-lead ECG within approximately 5 to 10 minutes total time
- ECHO/MUGA
- Ophthalmic examination
- Blood samples for the following tests:
    - Serum pregnancy test (females of childbearing potential only)
    - Clinical chemistry, coagulation and hematology
- Urine sample for urinalysis
- Review of concomitant medications
- Review of AEs
- Assess compliance with administration of encorafenib and binimetinib

8.3.4. Post-DDI Phase

It is recommended patients be evaluated according to standard practice. The following are provided as suggested time points for evaluation. In addition, efficacy assessment must be performed every 8-12 weeks in order to assess continued benefit.

8.3.4.1. Every 3-4 Weeks

- Review of concomitant medications
- Review of AEs with reporting of all Grade 3 or 4 AEs and all SAEs (follow-up of SAEs to continue as described in Section 10.1.3)
- Physical examination, hematology and chemistry laboratory testing
- If clinically indicated: triplicate 12-lead ECG within approximately 5 to 10 minutes total time

- Assess compliance with administration of encorafenib and binimetinib

8.3.4.2. Every 8-12 Weeks

- Efficacy assessment in order to assess continued benefit
- ECHO/MUGA (more frequent if clinically indicated)
- Ophthalmic examination (and as clinically indicated if visual symptoms are reported)
- Dermatologic examination every 8 weeks to be continued up to 6 months after discontinuing encorafenib

8.3.5. Day 30 Safety Follow-up Visit (Approximately 30 Days After Last dose of Study Drug)

- Review of concomitant medications
- Review of AEs with reporitng of all Grade 3 or 4 AEs and all SAEs (follow-up of SAEs to continue as described in Section 10.1.3)

Table 7. Schedule of Events – Arms 1 and 2

Study Procedures	Prescreen	Screen	DDI Phase								Post DDI Phase	
Days →	-57 to -36	-35 to -8	Day -7, Day 1 and Day 14							Day 28 / End of DDI Phase Treatment[a]	Every 3-4 weeks[b]	Day 30 Safety Follow-up Visit[c]
Hours →			0	1	2	3	4	6	8			
Mutation Prescreen Consent[d]	X											
Tumor Sample[d]	X											
Confirm *BRAF* Mutation Status[d]		X										
Informed Consent		X										
CCI [redacted]		[redacted]										
Disease Assessments (imaging and /or caliper measurements)[e]		X										
Inclusion/Exclusion Criteria[f]		X	X									
Demographics		X										
Medical History[g]		X										
Prior Treatments[h]		X										
Full Physical Examination		X								X	X[i]	
RECIST v1.1		X										
ECOG PS		X										
Height		X										
Weight		X	X							X		
Vital Signs[j]		X	X		X		X	X	X	X		
Triplicate 12-Lead ECG[k]		X	X		X		X	X	X	X	X	
ECHO/MUGA[l]		X								X	X	
Ophthalmic Examination [m]		X								X	X	
Hematology		X	X							X	X	
Clinical Chemistry		X	X							X	X	
Coagulation		X	X							X		
Urinalysis[n]		X	X							X		
Pregnancy Test[o]		X	X							X		
Serum FSH[o]		X										
AE Monitoring[b]		X	X	X	X	X	X	X	X	X	X	X

Table 7. Schedule of Events – Arms 1 and 2

Study Procedures	Prescreen	Screen	DDI Phase								Post DDI Phase	
Days →	-57 to -36	-35 to -8	Day -7, Day 1 and Day 14							Day 28 / End of DDI Phase Treatment[a]	Every 3-4 weeks[b]	Day 30 Safety Follow-up Visit[c]
Hours →			0	1	2	3	4	6	8			
Concomitant Medication Monitoring		X	X							X	X	X
Probe Cocktail Administration (Arm 1)			X									
Rosuvastatin and Bupropion Administration (Arm 2)			X									
Encorafenib QD/ Binimetinib BID Administration[p]			X									
Urine for PK[q,r]			X	X	X	X	X	X	X			
Blood for PK[s]			X	X	X	X	X	X	X			
Confinement in the CRU[t]			X	X	X	X	X	X	X			
Encorafenib / Binimetinib – Dispense and /or Assess Compliance[s]			X							X	X	
Determine BOR per Investigator and date of progression												X

AE = adverse event; BOR = best overall response; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Conference Oncology Group Performance Status; FDA = United States Food and Drug Administration; MRI = magnetic resonance imaging; PK = pharmacokinetic;

a Performed on those patients who discontinue the DDI phase prior to Day 28 and those patients who choose not to continue in the post-DDI phase.

b Patients who continue in the post-DDI phase will only be followed for safety. Safety should be monitored by assessing physical examination, hematology and chemistry laboratory testing and any other pertinent testing required as part of the safety profile of the compound (ophthalmic exams, cardiac profiles) until discontinuation. Investigators will be required to report any Grade 3-4 AEs and all SAEs as described in Section 10.1.3.

c Day 30 Safety Follow-up Visit to occur approximately 30 days after the last dose of study drug. Additional safety assessments may be performed at the Day 30 Safety Follow-up Visit to monitor any safety concerns identified during the safety follow-up phase.

d Fresh or archive tumor biopsy if prior documentation of *BRAF* mutation is not available. Analysis of *BRAF* mutation will be determined by local laboratory.

e Baseline disease assessments based on RECIST v1.1 (imaging and /or caliper measurements; can be up to Day -49 but must be confirmed by Day -7; if a patient has had an imaging assessment up to 6 weeks prior to Day -7 [Day -49 to Day -7], repeat assessment is not required).

f Eligibility criteria to be collected at screening and reconfirmed on Day -7 at Hour 0.

g Medical history includes alcohol and nicotine history over the 3 months before screening.

h All prior cancer treatments are to be recorded; other prior treatments (i.e., other than cancer treatments) taken within 4 weeks of screening should also be recorded.

i A dermatological exam is recommended to be performed every 8 weeks and up to 6 months after discontinuation of encorafenib.

j Vital signs include blood pressure, pulse rate, and temperature.

Table 7. Schedule of Events – Arms 1 and 2

Study Procedures	Prescreen	Screen	DDI Phase								Post DDI Phase	
Days →	-57 to -36	-35 to -8	Day -7, Day 1 and Day 14							Day 28 / End of DDI Phase Treatment[a]	Every 3-4 weeks[b]	Day 30 Safety Follow-up Visit[c]
Hours →			0	1	2	3	4	6	8			

k Three 12-lead ECGs are to be performed over a period of 5 to 10 minutes. Triplicate 12-lead ECGs will be performed at predose (up to 30 minutes before any study drug administration) and for all protocol specified post-baseline assessments. Postdose ECGs are to be performed at all protocol specified post-baseline assessments (± 30 minutes). Triplicate 12-lead ECGs are to be performed during the post-DDI phase if clinically indicated.

l ECHO/MUGA to be performed at Screening and at EOT. In the post-DDI phase, it is recommended that ECHO/MUGA scans be performed approximately every 8 to 12 weeks or more frequently if clinically indicated.

m Ophthalmic examinations are to be performed as needed during on-study treatment phase and at EOT. In the post-DDI phase, it is recommended that ophthalmic examinations be conducted approximately every 8 to 12 weeks and as clinically indicated if visual symptoms are reported.

n Urine cotinine test at screening for Arm 1 only. Drug and alcohol screen only to be done on Day -7 at Hour 0.

o For females only. For females of childbearing potential serum pregnancy tests are to be performed at screening; serum or urine pregnancy tests may be performed at subsequent time points during the study. For postmenopausal females, serum FSH to be performed to confirm postmenopausal status.

p Encorafenib/binimetinib will be dosed daily beginning on Day 1.

q Urine PK for patients in Arm 1 only.

r The predose urine sample will be separate from subsequent samples. All urine collected over the 0 to 8 hour period will be pooled. All PK samples up to and including the 8-hour time point must be obtained within 15 minutes of the designated collection time. Predose PK samples must be obtained prior to, but within 30 minutes of, administration of any study drug or probe substrate.

s Confinement in unit or returns, as necessary.

t Encorafenib/binimetinib – dispense and/or assess compliance – not done on Day -7.

Table 8. Schedule of Events – Arm 3

Study Procedures	Prescreen	Screen	DDI Phase											Post DDI Phase	
Days →	-50 to -29	-28 to -1	Day 1 and Day 15[a]			Day 14 and Day 21							Day 28 / End of DDI Phase Treatment[b]	Every 3-4 weeks[c]	Day 30 Safety Follow-up Visit[d]
Hours →			0	2	4	0	1	2	3	4	6	8			
Mutation Prescreen Consent[e]	X														
Tumor Sample[e]	X														
Confirm *BRAF* Mutation Status[e]		X													
Informed Consent		X													
Disease Assessments (imaging and /or caliper measurements)[f]		X													
Inclusion/Exclusion Criteria[g]		X	X												
Demographics		X													
Medical History[h]		X													
Prior Treatments[i]		X													
Full Physical Examination		X											X	X[j]	
RECIST v1.1		X													
ECOG PS		X													
Height		X													
Weight		X	X			X							X		
Vital Signs[k]		X	X	X	X	X		X		X	X	X	X		
Triplicate 12-Lead ECG[l]		X	X	X	X	X		X		X	X	X	X	X	
ECHO/MUGA[m]		X											X	X	
Ophthalmic Examination[n]		X											X	X	
Hematology		X	X			X							X	X	
Clinical Chemistry		X	X			X							X	X	
Coagulation		X	X			X							X		
Urinalysis[o]		X	X			X							X		
Pregnancy Test[p]		X	X			X							X		
Serum FSH[p]		X													
AE Monitoring[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Monitoring		X	X			X							X	X	X
Modafinil QD Administration[q]			X			X									

Table 8. Schedule of Events – Arm 3

Study Procedures	Prescreen	Screen	DDI Phase											Post DDI Phase	
Days →	-50 to -29	-28 to -1	Day 1 and Day 15[a]			Day 14 and Day 21							Day 28 / End of DDI Phase Treatment[b]	Every 3-4 weeks[c]	Day 30 Safety Follow-up Visit[d]
Hours →			0	2	4	0	1	2	3	4	6	8			
Encorafenib QD/ Binimetinib BID Administration[r]			X			X									
Blood for PK[s]						X	X	X	X	X	X	X			
Confinement in the CRU[t]			X	X	X	X	X	X	X	X	X	X			
Dispense and /or Assess Compliance			X			X							X	X	
Determine BOR per Investigator and date of progression															X

AE = adverse event; BOR = best overall response; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Conference Oncology Group Performance Status; FDA = United States Food and Drug Administration; MRI = magnetic resonance imaging; PK = pharmacokinetic;

a Verification of eligibility criteria, weight, chemistry, coagulation, urinalysis, pregnancy test and concomitant medication monitoring only required for Day 1.

b Performed on those patients who discontinue the DDI phase prior to Day 28 and those patients who choose not to continue in the post-DDI phase.

c Patients who continue in the post-DDI phase will only be followed for safety. Safety should be monitored by assessing physical examination, hematology and chemistry laboratory testing and any other pertinent testing required as part of the safety profile of the compound (ophthalmic exams, cardiac profiles) until discontinuation. Investigators will be required to report any Grade 3-4 AEs and all SAEs as described in Section 10.1.3.

d Day 30 Safety Follow-up Visit to occur approximately 30 days after the last dose of study drug. Additional safety assessments may be performed at the Day 30 Safety Follow-up Visit to monitor any safety concerns identified during the safety follow-up phase.

e Fresh or archive tumor biopsy if prior documentation of *BRAF* mutation is not available. Analysis of *BRAF* mutation will be determined by local laboratory.

f Baseline disease assessments based on RECIST v1.1 (imaging and /or caliper measurements; can be up to Day -42 but must be confirmed by Day 1; if a patient has had an imaging assessment up to 6 weeks prior to Day 1 [Day -42 to Day 1], repeat assessment is not required).

g Eligibility criteria to be collected at screening and reconfirmed on Day 1 at Hour 0.

h Medical history includes alcohol and nicotine history over the 3 months before screening.

i All prior cancer treatments are to be recorded; other prior treatments (i.e., other than cancer treatments) taken within 4 weeks of screening should also be recorded.

j A dermatological exam is recommended to be performed every 8 weeks and up to 6 months after discontinuation of encorafenib.

k Vital signs include blood pressure, pulse rate, and temperature.

l Three 12-lead ECGs are to be performed over a period of 5 to 10 minutes. Triplicate 12-lead ECGs will be performed at predose (up to 30 minutes before any study drug administration) and for all protocol specified post-baseline assessments. Postdose ECGs are to be performed at all protocol specified post-baseline assessments (± 30 minutes). Triplicate 12-lead ECGs are to be performed during the post-DDI phase if clinically indicated.

m ECHO/MUGA to be performed at Screening and at EOT. In the post-DDI phase, it is recommended that ECHO/MUGA scans be performed approximately every 8 to 12 weeks or more frequently if clinically indicated.

n Ophthalmic examinations are to be performed as needed during on-study treatment phase and at EOT. In the post-DDI phase, it is recommended that ophthalmic examinations be conducted approximately every 8 to 12 weeks and as clinically indicated if visual symptoms are reported.

o Drug and alcohol screen only to be done on Day 1 at Hour 0.

p For females only. For females of childbearing potential serum pregnancy tests are to be performed at screening; serum or urine pregnancy tests may be performed at subsequent time points during the study. For postmenopausal females, serum FSH to be performed to confirm postmenopausal status.

Table 8. Schedule of Events – Arm 3

Study Procedures	Prescreen	Screen	DDI Phase									Post DDI Phase	
Days →	-50 to -29	-28 to -1	Day 1 and Day 15[a]			Day 14 and Day 21						Day 28 / End of DDI Phase Treatment[b]	Every 3-4 weeks[c]	Day 30 Safety Follow-up Visit[d]
Hours →			0	2	4	0	1	2	3	4	6	8			

q Modafinil will be administered once daily on Day 15 to Day 21.
r Encorafenib/binimetinib will be dosed daily beginning on Day 1.
s All PK samples up to and including the 8-hour time point must be obtained within 15 minutes of the designated collection time. Predose PK samples must be obtained prior to, but within 30 minutes of, administration of any study drug or probe substrate.
t Confinement in unit or returns, as necessary.

9. STUDY DISCONTINUATION

9.1. Treatment Discontinuation for Individual Patients

Patients may withdraw their consent to participate in the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. Patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information. Patients should notify the Investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is only from further receipt of study treatment or also from study procedures and/or posttreatment study follow-up and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law. Patient data collected up to the date of consent withdrawal will be included in the analyses. Any blood or tissue samples collected up to the date of consent withdrawal will be analyzed.

Wherever possible, the tests and evaluations listed for the Day 30 Safety Follow-up Visit should be carried out and an effort should be made to continue follow-up. The Sponsor should be notified of all study withdrawals through the designated eCRFs in a timely manner.

Patients meeting any of the following criteria should discontinue study drug treatment:

- Withdrawal of consent (no further participation and thus no further protected health information may be collected),
- Adverse event requiring discontinuation of study drugs or rendering the patient unsuitable for further treatment in the judgment of the Investigator (includes delay in the post-DDI phase of more than 28 days to restart treatment due to an AE),
- Progressive disease,
- Pregnancy,
- Significant protocol deviation that, in the opinion of the Investigator and/or Sponsor, renders the patient unsuitable for further study treatment,
- Lost to follow-up,
- Death,
- Discretion of Investigator,
- Study termination by Sponsor.

Please see Appendix 13 for alternative study measures to be followed during public emergencies, including the COVID-19 pandemic.

9.2. Replacement of Patients

Patients who discontinue or require a dose reduction of study drug(s), in particular, encorafenib prior to completion of the last PK sampling on Day 14 in Arms 1 and 2 or on Day 21 in Arm 3 may be considered unevaluable for PK analyses and may be replaced. If a patient misses 3 or more consecutive doses of encorafenib in any arm or 3 or more doses of modafinil in Arm 3 prior to completion of the last PK sampling on Day 14 in Arms 1 and 2 or on Day 21 in Arm 3 due to noncompliance, the patient may remain on treatment but may be replaced if limited data are available from the patient. In addition, patients who miss a dose of study drugs on any of the PK days, or who vomit within 4 hours after dosing on any of the PK days, may be replaced but may remain on treatment. All patients receiving at least one dose of study drug will be evaluated for safety.

10. SAFETY MONITORING: DEFINITIONS AND REPORTING

10.1. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 10.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the patient to discontinue the study drug.

The patient will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the Investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

10.1.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving study treatment), through and including a minimum of 30 calendar days, except as indicated below, after the last administration of the study treatment.

During the long-term follow-up period in this study for survival, only SAEs will be actively elicited and collected after completion of the active collection period described above. The SAEs identified during long-term follow-up will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study treatment.

Follow-up by the Investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the Investigator and Pfizer concurs with that assessment.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

If the patient withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a patient definitively discontinues or temporarily discontinues study treatment because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the patient has concluded study participation. However, if the Investigator learns of any SAE, including a death, at any

time after a patient has completed the study, and he/she considers the event to be reasonably related to the study treatment, the Investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

10.1.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period as described in Section 7.1.1. are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 10. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study treatment is considered as a new anticancer therapy for the purposes of SAE reporting.

10.1.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a patient during the active collection period, which begins after obtaining informed consent as described in Section 7.1.1, will be recorded on the AE section of the CRF.

The Investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the patient.

If a patient begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study drug is considered as a new anticancer therapy for the purposes of SAE reporting.

10.1.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

10.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. For each event, the Investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of

possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 10.

10.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and Investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

- An Investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

10.1.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study drug under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of Investigator awareness.

10.1.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female patient is found to be pregnant while receiving or after discontinuing study drug.
- A male patient who is receiving or has discontinued study drug exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study drug due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study drug by ingestion.
    - A male family member or healthcare provider who has been exposed to the study drug by ingestion then exposes his female partner prior to or around the time of conception.

The Investigator must report EDP to Pfizer Safety within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a patient or a patient's partner, the Investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study drug and until 3 months after the last dose.

- If EDP occurs in the setting of environmental exposure, the Investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the Investigator site file.

Follow up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study drug.

Additional information regarding the EDP may be requested by the Sponsor. Further follow up of birth outcomes will be handled on a case by case basis (eg, follow up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

10.1.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female patient is found to be breastfeeding while receiving or after discontinuing study drug.
- A female is found to be breastfeeding while being exposed or having been exposed to study drug (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study drug by inhalation or skin contact.

The Investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the patient enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the Investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

10.1.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study drug, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial patient's care.

The Investigator must report occupational exposure to Pfizer Safety within 24 hours of the Investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the Investigator site file.

10.1.6. Cardiovascular and Death Events

Not applicable.

10.1.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

10.1.8. Adverse Events of Special Interest

Not applicable.

10.1.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

10.1.9. Medical Device Deficiencies

Not applicable.

10.1.10. Medication Errors

Medication errors may result from the administration or consumption of the study drug by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Exposures to the study drug under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the AE CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	Only if associated with an AE or SAE	Only if associated with an SAE

Medication errors include:

- Medication errors involving patient exposure to the study drug;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study patient.

In the event of a medication dosing error, the Sponsor should be notified within 24 hours.

If applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

10.2. Treatment of Overdose

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the patient for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study treatment (whichever is longer). Closely monitor the patient for any AEs/SAEs.

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor Medical Monitor based on the clinical evaluation of the patient.

11. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1. General Considerations

A detailed statistical analysis plan (SAP) will be prepared by the Sponsor. This plan may modify the statistical methods outlined in the protocol; however, any major modifications of the primary endpoint definition or analysis will also be described in a protocol amendment.

11.1.1. Sample Size

For Arm 1, sample size was determined by the substrate in the CYP probe cocktail with the highest reported difference in standard deviation (Ryu et al. 2007). The coefficient of variation of the difference between 2 AUC_{last} values for the same patient for omeprazole is approximately 38%. Assuming a 2-sided significance level of 0.05 and a power of 0.8, approximately 20 patients would need to be evaluable to detect a difference of 25% in mean AUC_{last}. Additionally, these values are similar to other cocktail studies run in oncology patients (Goh 2010).

For Arm 2, the coefficient of variation of the ratio between 2 rosuvastatin AUC_{last} values for the same patient for rosuvastatin is approximately 47% (Stopfer 2016). Assuming a 2-sided significance level of 0.05 and a power of 0.8, approximately 10 patients would need to be evaluable to detect a difference of 50% in mean AUC_{last}. Assuming an intrasubject variation of 23% for bupropion AUC_{0-8} (Bosilkovska 2014), there is an 80% probability with 10 subjects that a treatment difference will be detected if the true effect size is 33%.

For Arm 3, PK data will be analysed after the first 6 patients to look for an indication that the moderate inducer is having a significant effect on encorafenib PK. If there is a $\geq$ 20% change in mean encorafenib AUC, then an additional 6 patients will be enrolled to more fully characterize the effect. Assuming an intrasubject variation of 36.4% for encorafenib AUC_{tau} (Clinical Study CMEK162X2110), there is an 80% probability with fixed sample sizes of 6 and 12 subjects that a treatment difference will be detected if the true effect size is 74 and 46%, respectively.

11.1.2. Safety Analysis

During the DDI phase, all safety data for all three arms will be recorded in the patient's source documents and eCRFs. Adverse events including SAEs, laboratory profiles (hematology, biochemistry, coagulation, cardiac/muscle enzymes, urinalysis), physical examination (including vital signs, ophthalmic and dermatological examinations), ECOG PS assessment, and cardiac profiles (ECG and MUGA or ECHO), concomitant medications and/or therapies will be recorded.

All patients who receive at least one dose of study drug will be included in the safety analyses.

Safety data from the DDI phase will be presented in tabular and/or graphical format and summarized descriptively by treatment group and study day, where appropriate. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Incidence tables will be presented for all AEs by maximum severity, SAEs, AEs assessed as

related to study drug and AEs resulting in discontinuation of study drug. Changes in ECG and laboratory measurements will be summarized. Listings of all safety data sorted by treatment group, patient and assessment date will be provided.

During the post-DDI phase, it is recommended that safety evaluations occur every 3 to 4 weeks, unless otherwise specified. Safety should be monitored by assessing physical examination, hematology and chemistry laboratory testing and any other pertinent testing required as part of the safety profile of the compound (dermatological examinations, ophthalmic exams, cardiac profiles) until discontinuation. Investigators will be required to report any SAEs to the Sponsor or designee using the SAE form.

11.1.3. Pharmacokinetic Analysis

Patients who have sufficient concentration data to calculate at least one PK parameter on Day -7, Day 1, Day 14 and Day 21 (as appropriate), will be included in the PK analyses. Plasma or urine concentrations of midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxy omeprazole, rosuvastatin, losartan, E-3174, dextromethorphan, dextrorphan, bupropion, hydroxybupropion, binimetinib, AR00426032, encorafenib and LHY746 will be determined using validated bioanalytical methods. Standard noncompartmental PK parameters will be estimated for each analyte in plasma by day and patient. For each analyte in urine, the Ae_{0-8}, the fe into urine and the renal clearance (CL_R) will be calculated. Descriptive statistics of PK parameters will be reported for each analyte by day. CCI [redacted] Remaining plasma PK samples from Arm 3 may also be analyzed for modafinil using either a nonvalidated or validated bioanalytical method.

For the primary analysis in Arms 1 and 2, an analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed C_{max} and AUC_{last} of midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxy omeprazole, rosuvastatin, bupropion and hydroxybupropion and the urine losartan, E-3174, dextromethorphan and dextrorphan Ae_{0-8}. For the primary analysis in Arm 3, an ANOVA will be performed on the encorafenib ln-transformed C_{max} and AUC. The ANOVA model will include treatment as fixed effect and patient as the random effect. Each ANOVA will include calculation of least squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference.

Ratios of LSM will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed parameters. In Arms 1 and 2, these ratios will be expressed as a percentage of Day 1 (test) relative to Day -7 (reference), Day 14 (test) relative to Day 1 (reference) and Day 14 (test) relative to Day -7 (reference). In Arm 3, these ratios will be expressed as a percentage of Day 21 (test) relative to Day 14 (reference).

Consistent with the 2 one-sided test, 90% confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the analyses on the ln-transformed parameters. In Arms 1 and 2, the CIs will be expressed as a percentage of Day 1 (test) relative to Day -7 (reference), Day 14 (test)

relative to Day 1 (reference) and Day 14 (test) relative to Day -7 (reference). In Arm 3, these ratios will be expressed as a percentage of Day 21 (test) relative to Day 14 (reference).

Similarly, an ANOVA will be performed on the ln-transformed MR_{AUC} and MR_{Cmax} calculated for 1-OH midazolam/midazolam, paraxanthine/caffeine, 5-hydroxy omeprazole/omeprazole, hydroxybupropion/bupropion and LHY746/encorafenib and MR_{Ae0-8} for E-3174/losartan and dextrorphan/dextomethorphan.

Additional modeling of PK data using alternate methodologies (e.g., compartmental, population-based nonlinear mixed effects models or physiologically-based PK methods) may be conducted. Results will be reported separately.

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12. DATA RECORDING, RETENTION AND MONITORING

12.1. Case Report Forms

Data will be collected using (source documents/an electronic data capture system [EDC]) at the clinical site. The Investigator or designee will record data specified in the protocol using eCRFs. Changes or corrections to eCRFs will be made by the Investigator or an authorized member of the study staff according to the policies and procedures at the site.

It is the Investigator's responsibility to ensure eCRFs are complete and accurate. Following review and approval, the Investigator will electronically sign and date the pages. This signature certifies that the Investigator has thoroughly reviewed and confirmed all data on the eCRF.

A portable document format (PDF) file of the eCRFs will be provided to the site after all data have been monitored and reconciled. An electronic copy will be archived at the site.

12.2. Data Monitoring

This study will be closely monitored by representatives of the Sponsor throughout its duration. Monitoring will include personal visits with the Investigator and study staff as well as appropriate communications by telephone, fax, mail, email or use of the EDC system, if applicable. It is the monitor's responsibility to inspect eCRFs at regular intervals throughout the study to verify the completeness, accuracy and consistency of the data and to confirm adherence to the study protocol and to GCP guidelines. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of this study are resolved promptly. The Investigator and site will permit study-related monitoring, audits, EC review and regulatory inspection, including direct access to source documents.

It is understood that study monitors and any other personnel authorized by the Sponsor may contact and visit the Investigator and will be permitted to inspect all study records (including eCRFs and other pertinent data) on request, provided that patient confidentiality is maintained and that the inspection is conducted in accordance with local regulations.

Every effort will be made to maintain the anonymity and confidentiality of patients during this study. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor as well as authorized representatives of regulatory authorities to inspect the facilities used in the conduct of this study and to inspect, for purposes of verification, the hospital or clinic records of all patients enrolled in the study.

12.3. Quality Control and Quality Assurance

Quality control procedures will be conducted according to the Sponsor's internal procedures. The study site may be audited by a quality assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

13. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

13.1. Good Clinical Practice

The study will be performed in accordance with the protocol, guidelines for Good Clinical Practice (GCP) established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and applicable local regulatory requirements and laws.

13.2. Ethics Committee Approval

The Investigator must inform and obtain approval from the EC for the conduct of the study at named sites, the protocol, informed consent documents and any other written information that will be provided to the patients and any advertisements that will be used. Written approval must be obtained prior to recruitment of patients into the study and shipment of study drug.

Proposed amendments to the protocol and aforementioned documents must be submitted to the Sponsor for review and approval, then to the EC. Amendments may be implemented only after a copy of the approval letter from the EC has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Per GCP guidelines, the Investigator will be responsible for ensuring that an annual update is provided to the EC to facilitate continuing review of the study and that the EC is informed about the end of the study. Copies of the update, subsequent approvals and final letter must be sent to the Sponsor.

13.3. Regulatory Authority Approval

The study will be performed in accordance with the requirements of [each country's regulatory authorities, e.g., U.S. FDA and Health Canada] and will also meet all of the requirements of ICH GCP guidance. Amendments to the protocol will be submitted to the [relevant authorities, e.g. FDA or Health Canada] prior to implementation in accordance with applicable regulations.

13.4. Other Required Approvals

In addition to EC and regulatory authority approval, all other required approvals (e.g. approval from the local research and development board or scientific committee) will be obtained prior to recruitment of patients into the study and shipment of study drug.

13.5. Informed Consent

Informed consent is a process that is initiated prior to the patient's agreeing to participate in the study and continues throughout the patient's study participation. It is the Investigator's responsibility (or designee) to obtain written informed consent from each patient after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any study procedures are initiated. Each patient should be given a copy of

the informed consent document and associated materials. The original copy of the signed and dated informed consent document must be retained at the site and is subject to inspection by representatives of the Sponsor or regulatory authorities. If any amendments occur throughout the course of the study that affect the informed consent form (i.e. when new study procedures or assessments have been added), all active patients should be re-consented using the same process for the initial consent.

13.6. Patient Confidentiality

The Investigator must ensure that the patient's privacy is maintained. On the eCRF or other documents submitted to the Sponsor, patients will be identified by a patient number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent documents) should be kept in a confidential file by the Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory authorities and ethics committees to review the portion of the patient's medical record that is directly related to the study. As part of the required content of informed consent documents, the patient must be informed that his/her records will be reviewed in this manner.

13.7. Disclosure of Information

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the study only.

It is understood by the Investigator that the Sponsor will use information obtained in this clinical study in connection with the clinical development program, and therefore may disclose it as required to other clinical Investigators and to regulatory authorities. In order to allow the use of the information derived from this clinical study, the Principal Investigator understands that he/she has an obligation to provide complete test results and all data obtained during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

13.8. Publication of Study Data

The conditions regulating dissemination of the information derived from this study are described in the Clinical Trial Agreement.

13.8.1. Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bonafide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

14. ADHERENCE TO THE PROTOCOL

Investigators must apply due diligence to avoid protocol deviations, and the Sponsor (and designee[s]) will not pre-authorize deviations. If the Investigator believes a change to the protocol would improve the conduct of the study, this must be considered for implementation in a protocol amendment. Protocol deviations will be recorded.

14.1. Amendments to the Protocol

Only the Sponsor may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor and the Investigator. The only exception is when the Investigator considers that a [subject's/patient's] safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the EC must be sought, and the Investigator should inform the Sponsor and the full EC within 5 working days after the emergency occurred. All amendments that have an impact on [subject/patient] risk or the study objectives or require revision of the informed consent document must receive approval from the EC prior to implementation.

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Appendix 1. Recommended Guidelines for the Management of Encorafenib-Induced and/or Binimetinib-Induced Skin Toxicity

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In general, the following interventions are in addition to the encorafenib-induced and/or binimetinib-induced rash dosing guidelines provided in Table 5, respectively, of the protocol.

The Initial Rash Treatment Regimen may be initiated as prophylactic treatment 24 hours prior to the first treatment, or later as needed to treat mild rash (CTCAE Grade 1).

Initial Rash Treatment Regimen:

- Application of topical agents to the most commonly affected skin areas such as face, scalp, neck, upper chest and upper back. Topical agents include the following:
    - Non-oily sunscreen (PABA-free, SPF ≥ 30, UVA/UVB protection);
    - Topical steroids, preferably mometasone cream (e.g., Elocon®);
    - Topical erythromycin (e.g., Eryaknen®);
    - Topical pimocrolimus.

Note: Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to first treatment, and more often as needed.

- Possibly oral doxycycline (100 mg daily) for the first 2 to 3 weeks of study drug administration.

Other effective medications are antihistamines, other topical corticosteroids, other topical antibiotics and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

Mild Rash (CTCAE Grade 1) Treatment Regimen:

- Initiate Initial Rash Treatment Regimen, if not already started.
- Use of topical corticosteroid (e.g., mometasone cream) and/or topical antibiotic (e.g., erythromycin 2%) is recommended.
- The patient should be reassessed within a maximum of 2 weeks, or as per Investigator opinion.

Moderate Rash (CTCAE Grade 2) Treatment Regimen:

- Use of topical erythromycin or clindamycin (1%) plus topical mometasone or topical pimecrolimus (1% cream) plus oral antibiotics, such as lymecycline (408 mg QD), doxycycline (100 mg BID) or minocycline (50 to 100 mg BID).

- Although there has been no evidence of phototoxicity or photosensitivity in patients treated with binimetinib, doxycycline (or minocycline as second line) should be used with thorough UV protection (i.e., avoidance of direct exposure to sunlight, use of sunscreen and sunglasses, etc.).

- Use of acitretin is not recommended.

Severe Rash (CTCAE Grade 3-4) Treatment Regimen:

CTCAE Grade 3:

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner (25 mg for 7 days, subsequently decreasing the dose by 5 mg/day every day).

- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low dose, i.e., 0.3 to 0.5 mg/kg) (Lacouture et al. 2011).

- Use of acitretin is not recommended.

CTCAE Grade 4 Treatment Regimen:

- Immediately discontinue the patient from study drug and treat the patient with oral or topical medications (see recommendation CTCAE Grade 3).

Symptomatic Treatment Regimen:

It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment:

- For pruritic lesions: use cool compresses and oral antihistamine agents.

- For fissuring: use Monsel's solution, silver nitrate or zinc oxide cream. If not sufficient, use mild corticosteroid ointments or ointments containing a combination of corticosteroid and antibiotic such as Fucicort®.

- For desquamation: use emollients that are mild pH 5/neutral (recommended to contain 10% urea).

- For paronychia: use antiseptic bath and local potent corticosteroids, use oral antibiotics, and, if no improvement is seen, refer to a dermatologist or surgeon.

- For infected lesions: obtain bacterial and fungal cultures and treat with topical or systemic antibiotics, if indicated, based on sensitivity of culture.

References:

Lacouture ME, Anadkat MJ, Bensadoun RJ et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 2011;19:1079–95.

Appendix 2. Recommended Guidelines for the Management of Encorafenib-Induced Hand-Foot Skin Reactions (HFSR)

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In addition to the HFSR dosing guidelines in Table 5 of the protocol, the following algorithm is recommended for the management of HFSR based on the severity of HFSR (adapted from Nardone et al. 2012).

Algorithm for the Management of HFSR Based on the Severity of HFSR

HFSR severity	**Intervention**
No HFSR	**Maintain Frequent Contact with physician to ensure early diagnosis of HFSR**
Therapy initiation	Full body-skin examination, pedicure, evaluation by podiatrist or orthotist; wear thick cotton gloves and/or socks; avoid hot water, constrictive footwear and excessive friction
	If symptoms develop, proceed to next step
↓	
Grade 1	**Maintain current dose of BRAF inhibitor; monitor patient for change in severity**
Minimal skin changes or dermatitis without pain e.g.: • Numbness • Tingling • Dysesthesia • Paresthesia • Erythema • Edema • Hyperkeratosis No interference with ADL	Avoid hot water; use moisturizing cream for relief; wear thick cotton gloves and/or socks; use a 20-40% urea , salicylic acid 3-6%; ammonium lactate 12 % or lactic acid 12 % based creams to aid exfoliation.
	If symptoms worsen, proceed to next steps
↓	
Grade 2	**Maintain current dose of BRAF inhibitor; monitor patient for change in severity**
Skin changes with pain e.g. Peeling • Blisters • Bleeding • Edema • Hyperkeratosis Limited instrumental ADL	Treat as with Grade 1 toxicity, with the following additions: clobetasol 0.05% ointment, 2-4% lidocaine, opiates, NSAIDS, or GABA agonists for pain; follow dose modifications listed in Table 5
	If no improvement within 15 days, proceed to next steps.
↓	

HFSR severity	Intervention
Grade 3	**Interrupt dose until improvement to Grade 0-1**
Severe skin changes with pain e.g. Peeling ● Blisters ● Bleeding ● Edema ● Hyperkeratosis Limiting self-care ADL	Treat as in Grades 1 and 2 Follow dose modifications listed in Table 5.

The following supportive care measures for the prevention, and/or management of HFSR summarized in the table below should be instituted along with proper patient education.

Supportive Care for the Prevention and Management of HFSR

Stage	Recommendations
Prior to initiation of study treatment	Educate the patient about the early signs and symptoms of HFSR and discuss the importance of early reporting. HFSR could start as early as 2-5 days after study drug initiation, and mostly expected to occur during the first 2 months of treatment.
Prevention of HFSR for the first 2 months of treatment with encorafenib	Monitor the patient for signs and symptoms of HFSR. Instruct the patient to: - Apply emollient cream regularly to hands and feet: use 20-40% urea , salicylic acid 3-6%; ammonium lactate 12% or lactic acid 12 % based creams - Wear cotton socks or gloves to bed to enhance the absorption of creams - Avoid tight, irritating or ill-fitting clothing and shoes - Avoid repetitive activity or staying in one position for long periods of time - Pat (do not rub) skin dry with towels - Avoid extremes of temperature, pressure and friction - Avoid performing mechanically stressful manual work - Cushioning of callused areas - Use of moisturizing and keratolytic creams to control existing palmar and plantar hyperkeratosis
Treatment of HFSR	1) Ensure that patient follows treatment interruption or dosage reduction guidelines 2) Monitor the patient for worsening/resolution of HFSR (Normal frequency monthly, except if patient has Grade 2 or 3 HFSR, where bi weekly- visits are recommended) 3) Prescribe analgesics if necessary 4) Instruct the patient to: - Continue the use of prevention strategies - Cushion sore skin - For control or relief of pain symptoms, patient may submerge hands and feet in cool water baths or apply cold compresses for relief

a Wear loose-fitting clothing made of soft, natural fabrics and shoes that are wide and comfortable. Avoid tight belts, panties and bras.
This table is adapted from (van Moos et al. 2008).

References:

Nardone B, Hensley JR, Kulik L, et al. (2012). The effect of hand-foot skin reaction associated with the multikinase inhibitors sorafenib and sunitinib on health-related quality of life. Journal of Drugs in Dermatology Nov 2011: 11;11:e61-5.

Van Moos R, Thuerlimann B, Chair M, etal. (2008) Pegylated liposomal doxorubicin-associated hand-foot syndrome: Recommendations of an international panel of experts. Eur J Cancer: 1016:1-10.

Appendix 3. Recommended Guidelines for the Management of Binimetinib-Induced Diarrhea

Proactively Investigate for Occurrence of Diarrhea and Educate Patient:

1. Remind patients at each visit to contact the Investigator immediately upon the first sign of loose stool or symptoms of abdominal pain. Additionally, at each study visit, each patient should be asked regarding occurrence of diarrhea or diarrhea-related symptoms. If the patient has had symptoms, the patient should be asked regarding the actions taken for these symptoms and re-instruct if indicated.

2. Patients should be instructed on dietary modification and early warning signs of diarrhea and potentially life-threatening illnesses (e.g., severe cramping might be a sign of severe diarrhea; fever with diarrhea might be a sign of infection; fever and dizziness on standing might be a sign of shock).

3. Patients should be educated about what to report to the Investigator (i.e., number of stools, stool composition, stool volume).

Anti-diarrhea Therapy:

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as outlined above, as well as proper management of diarrhea is important.

Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. All concomitant therapies /used for treatment of diarrhea must be recorded on the eCRF. It is recommended that patients be provided loperamide tablets and be instructed on the use of loperamide on the first day of binimetinib dosing. In addition to the binimetinib-induced diarrhea dosing guidelines provided in Table 5 of the protocol, these instructions should be provided at each visit and the site should ensure that the patient understood the instructions.

See Table 5 in the protocol to explain the frequency of diarrhea and its relationship to NCI CTCAE, v.4.03 grading and to determine if diarrhea is complicated or uncomplicated.

Rule out Other or Concomitant Causes:

These may include:

- Infection with *Candida, Salmonella, Clostridium difficile, Campylobacter. Giardia, Entamoeba* or *Cryptosporidium* species, which can lead to severe infections in immunosuppressed patients.

- Medication-induced diarrhea.

- Malabsorption/lactose intolerance.

- Fecal impaction, partial bowel obstruction.

For Uncomplicated Grade 1/2 Diarrhea:

- Stop all lactose-containing products and alcohol, and eat frequent small meals that include bananas, rice, applesauce or toast.
- Stop laxatives, bulk fiber (e.g., Metamucil®), and stool softeners (e.g., docusate sodium, Colace®).
- Stop high-osmolar food supplements (e.g., Ensure® Plus, Jevity® Plus [with fiber]).
- Drink 8 to 10 large glasses of clear liquids per day (e.g., water, Pedialyte®, Gatorade®, broth).
- Consider administration of a standard dose of loperamide: initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Discontinue loperamide after 12-hours diarrhea-free (Grade 0) interval.
- Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Re-treatment may then be resumed at current dose level.
- If uncomplicated Grade 1 to Grade 2 diarrhea persists for more than 24 hours, escalate to high-dose loperamide: 2 mg every 2 hours (maximum of 16 mg/day) or after each unformed stool.

Note: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

- If uncomplicated Grade 1 to Grade 2 diarrhea persists after 48 hours of treatment with loperamide, discontinue loperamide and begin a second-line agent which can be an opiate (opium tincture or paregoric), octreotide acetate or steroid (budesonide).

For Complicated Grade 1/2 Diarrhea or Any Grade 3/4 Diarrhea:

- The patient must call the Investigator immediately.
- Temporarily interrupt binimetinib treatment until resolved to Grade ≤ 1. Restart binimetinib at a reduced dose level.
- If loperamide has not been intitiated, initiate loperamide immediately. Initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool.
- Administer IV fluids and electrolytes as needed. In case of severe hydration, replace loperamide with octreotide acetate.

- Monitor/continue IV fluids and antibiotics as needed. Intervention should be continued until the patient is diarrhea-free for at least 24 hours.

- Hospitalization may need to be considered.

Appendix 4. Recommended Guidelines for the Management of Binimetinib-Induced Interstitial lung disease

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In general, the following interventions are in addition to the binimetinib-induced interstitial lung disease (ILD) dosing guidelines provided in Table 5 of the protocol.

Drug-induced ILD or pneumonitis is a clinical diagnosis based on clinical signs and symptoms, radiological changes, pulmonary function tests (PFT) and exclusion of other possible etiologies of parenchymal lung disease. The most common symptoms of ILD are nonspecific and include dyspnea, dry cough, fever, fatigue, hypoxia, and occasional hemoptysis. The CTCAE v.4.03 criteria for ILD (pneumonitis) are provided below.

CTCAE v. 4.03 Criteria for Pneumonitis					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death

Definition: A disorder characterized by inflammation or diffusely affecting the lung parenchyma.

All patients should be instructed to immediately report new or worsening respiratory symptoms. Diagnostic procedures include PFT and high-resolution CT scans (HCRT). The principal management of ILD consists of drug interruption and/or dose reduction and treatment with steroids as specified below. Empirical antibiotics directed at likely pathogens should also be considered while the results of diagnostic procedures and cultures are pending.

- Prednisolone 40 mg oral, daily
    - Reduce dose by 10 mg every 2 weeks × 2 (until dose reduced to 20 mg oral, daily)
    - Reduce dose by 5 mg weekly × 4 weeks
- Combine with empirical antimicrobial therapy while awaiting results of diagnostic procedures

Reference: Shah R. Tyrosine kinase inhibitor-induced interstitial lung disease: Clinical features, diagnostic challenges, and therapeutic dilemmas. Drug Saf. 2016;39:1073-1091.

Appendix 5. Snellen Equivalence (Visual Acuity Conversion Chart)

				Distance				Near					
					Snellen Equivalent								
Line Number	Visual Angle (min)	Spatial Frequency (Cyc/deg)	LogMAR	% Central Visual Efficiency	Feet 20/	Meter 6/	Decimal	% Central Visual Efficienty	Inches (14/)	Centimeters (35/)	Revised Jaeger Standard	American Point-Type	"M" Notation
−3	0.50	60.00	0.30	100	10	3.0	2.00	100	7.0	17.5	—	—	0.20
−2	0.63	48.00	0.20	100	12.5	3.8	1.60	100	8.8	21.9	—	—	0.25
−1	0.80	37.50	0.10	100	16	4.8	1.25	100	11.2	28.0	—	—	0.32
0	1.00	30.00	0.00	100	20	6.0	1.00	100	14.0	35.0	1	3	0.40
1	1.25	24.00	−0.10	95	25	7.5	0.80	100	17.5	43.8	2	4	0.50
—	1.50	20.00	−0.18	91	30	9.0	0.67	95	21.0	52.5	3	5	0.60
2	1.60	18.75	−0.20	90	32	9.6	0.63	94	22.4	56.0	4	6	0.64
3	2.00	15.00	−0.30	85	40	12.0	0.50	90	28.0	70.0	5	7	0.80
4	2.50	12.00	−0.40	75	50	15.0	0.40	50	35.0	87.5	6	8	1.0
—	3.00	10.00	−0.48	67	60	18.0	0.33	42	42.0	105.0	7	9	1.2
5	3.15	9.52	−0.50	65	63	18.9	0.32	40	44.1	110.3	8	10	1.3
—	3.50	8.57	−0.54	63	70	21.0	0.29	32	49.0	122.5	—	—	1.4
6	4.00	7.50	−0.60	60	80	24.0	0.25	20	56.0	140.0	9	11	1.6
7	5.00	6.00	−0.70	50	100	30.0	0.20	15	70.0	175.0	10	12	2.0
—	5.70	5.26	−0.76	44	114	34.2	0.18	12	79.8	199.5	11	13	2.3
8	6.25	4.80	−0.80	40	125	37.5	0.16	10	87.5	218.8	12	14	2.5
—	7.50	4.00	−0.88	32	150	45.0	0.13	6	105.0	262.5	—	—	3.0
9	8.00	3.75	−0.90	30	160	48.0	0.13	5	112.0	280.0	13	21	3.2
10	10.00	3.00	−1.00	20	200	60.0	0.10	2	140.0	350.0	14	23	4.0
11	12.50	2.40	−1.10	17	250	75.0	0.08	0	175.0	437.5	—	—	5.0
—	15.00	2.00	−1.18	16	300	90.0	0.07	0	210.0	525.0	—	—	6.0
12	16.00	1.88	−1.20	15	320	96.0	0.06	0	224.0	560.0	—	—	6.4
13	20.00	1.50	−1.30	10	400	120.0	0.05	0	280.0	700.0	—	—	8.0
16	40.00	0.75	−1.60	5	800	240.0	0.03	0	560.0	1400.0	—	—	16.0
20	100.00	0.30	−2.00	0	2000*	600.0	0.01	0	1400.0	3500.0	—	—	40.0
30	1000.00	0.03	−3.00	0	20000†	6000.0	0.001	0	14000.0	35000.0	—	—	400.0

Bold values are standard logMAR progression.
LogMAR = logarithm of the minimum angle of resolution
*20/2000 is equivalent to counting fingers @ 2 feet
†20/20000 is equivalent to hand motion @ 2 feet

References:

Holladay JT. Visual acuity measurements. J Cataract Refract Surg. 2004;30:287-90.

Appendix 6. List of Concomitant Medications

Table A: List of CYP450 Substrates to be Used With Caution*

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
Amodiaquine	Acenocoumarol	Clopidogrel	Alfentanil [1,2]	Ergotamine [2]
Cerivastatin	Celecoxib	Diazepam	Alpha-dihydroergocryptine [1]	Everolimus [1]
Repaglinide	Diclofenac	Esoprazole	Alprazolam	Felodipine [1]
Rosiglitazone	Glipizide	Lansoprazole	Amlodipine	Fentanyl [2]
Torasemide	Irbesartan	Moclobemide	Aplaviroc	Fluticasone [1]
	Losartan	Omeprazole	Aprepitant [1]	Indinavir [1]
	Phenytoin [2]	Pantoprazole	Aripiprazole	Lopinavir [1]
	Piroxicam	Phenobarbitone	Atorvastatin	Lovastatin [1]
	S-ibuprofen	Phenytoin [2]	Boceprevir	Maraviroc [1]
	Sulfamethoxazole	Proguanil	Brecanavir	Midazolam [1]
	Tolbutamide	Rabeprazole	Brotizolam [1]	Nifedipine
	Torasemide	S-mephenytoin	Budesonide [1]	Nisoldipine
			Buspirone [1]	Nitrendipine
			capravirine	Perospirone [1]
			casopitant	Quinine
			Conivaptan [1]	Saquinavir [1]
			Cyclosporine [2]	Sildenafil [1]
			Darifenacin [1]	Simvastatin [1]
			Darunavir [1]	Sirolimus [1,2]
			Diazepam	Telaprevir
			Diergotamine [2]	Tipranavir [1]
			Diltiazem	Tolvaptan
			Ebastine [1]	Triazolam [1]
			Eletriptan [1]	Verapamil
			Eplerenone [1]	

*Table was compiled from the Indiana University School of Medicine's "Clinically Relevant" table, a list by the United States Food and Drug Administration (FDA) fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm, and the University of Washington's Drug Interaction Database.
[1] Sensitive substrates: Drugs whose plasma area under concentration-time curve (AUC) values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.
[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., TdP).

Table B: List of CYP450 Substrates to be Used With Caution – CYP2B6

CYP2B6*
bupropion [1]
cyclophosphamide
Efavirenz [1]
Ifosfamide
Methadone
Thiotepa

*Table was compiled from the Indiana University School of Medicine's "Clinically Relevant" table, a list by the FDA (http://.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm) and the University of Washington's Drug Interaction Database.
[1] Sensitive substrates: The area under the concentration-time curves (AUCs) of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

Table C: Strong/moderate CYP3A4 Inhibitors and CYP3A4 Inducers to be Prohibited or Administered With Caution when Co-administered with Encorafenib

Strong Inhibitors (prohibited)	
boceprevir	nefazodone
Clarithromycin	Nelfinavir
Conivaptan	posaconazole
Indinavir	Ritonavir
Itraconazole	Saquinavir
Ketoconazole	telithromycin
Lopinavir	troleandomycin
Telaprevir	Grapefruit juice (citrus paradisi fruit juice)
Mibefradil	Voriconazole
Moderate inhibitors (use with caution)	
Ciprofloxacin	Erythromycin
Fluconazole	Amprenavir
Verapamil	Imatinib
Atazanavir	Schisandra sphenanthera
Aprepitant	Casopitant
Cyclosporine	Cimetidine
Tofisopam	Dronedarone
Fosamprenavir	Darunavir
Diltiazem	
Strong Inducers (use with caution)	
Avasimibe	Rifampin
Carbamazepine	St. John's wort
Phenytoin	

Reproduced from
fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Table D: Substrates of BCRP, OAT, OCT s and OATPs to be Administered With Caution

	Substrates
BCRP	imatinib, irrinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
OCT2	Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin
OAT1	Adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine
OAT3	Acyclovir, bumetanide, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, oseltamivir acid, (the active metabolite of oseltamivir), penicillin G, pravastatin, rosuvastatin, sitagliptin
OATP1B1	Atrasentan, atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, SN-38 (active metabolite of irinotecan), rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan
OATP1B3	Atorvastatin, rosuvastatin, pitavastatin, telmisartan, valsartan, olmesartan

Reproduced from
fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Table E: Pg-P and BCRP Inhibitors/Inducers to be Used With Caution

Transporter	Gene	Inhibitor [1]	Inducer [2]
P-gp	ABCB1	Amiodarone, azithromycin,captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	Avasimibe,carbamazepine,phenytoin, rifampin, St John's wort, tipranavir/ritonavir
BCRP	ABCG2	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known

Reproduced from
fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

1. Inhibitors listed for P-gp are those that showed > 25% increase in digoxin area under the concentration-time curve (AUC) or otherwise indicated if substrate is other than digoxin.
2. Inducers listed for P-gp are those that showed > 20% decrease in digoxin AUC or otherwise indicated if substrate is other than digoxin.

Table F: List of Inhibitors of UGT1A1 to be Used With Caution

Inhibitors of UGT1A1	atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib

Table G: List of Potential QT Prolonging Drugs

Drug	QT risk*	Comment
Alfuzosin	possible risk	
Amantadine	possible risk	
Amiodarone	known risk	Females > Males, TdP risk regarded as low
Amitriptyline	conditional risk	Risk of TdP with overdosage. Substrate of CYP2C19
Arsenic trioxide	known risk	
Astemizole	known risk	No Longer available in U.S. Substrate for 3A4
Atazanavir	possible risk	
Azithromycin	possible risk	Rare reports
Bepridil	known risk	Females > Males
Chloral hydrate	possible risk	
Chloroquine	known risk	
Chlorpromazine	known risk	
Ciprofloxacin	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Cisapride	known risk	No longer available in the U.S.; available in Mexico. Substrate for 3A4
Citalopram	known risk	
Clarithromycin	known risk	Substrate for 3A4
Clomipramine	conditional risk	
Clozapine	possible risk	
Desipramine	conditional risk	Risk of TdP with overdosage
Diphenhydramine	conditional risk	Risk of QT increase/TdP in overdosages
Disopyramide	known risk	Females > Males
Dofetilide	known risk	
Dolasetron	possible risk	
Domperidone	known risk	Not available in the U.S.
Doxepin	conditional risk	
Dronedarone	possible risk	Substrate for 3A4
Droperidol	known risk	
Eribulin	possible risk	
Erythromycin	known risk	Females>Males. Substrate for 3A4
Escitalopram	possible risk	
Famotidine	possible risk	
Felbamate	possible risk	
Fingolimod	possible risk	
Flecainide	known risk	
Fluconazole	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Fluoxetine	conditional risk	
Foscarnet	possible risk	
Fosphenytoin	possible risk	
Galantamine	conditional risk	
Gatifloxacin	possible risk	
Gemifloxacin	possible risk	
Granisetron	possible risk	
Halofantrine	known risk	Females>Males

Table G: List of Potential QT Prolonging Drugs

Drug	QT risk*	Comment
Haloperidol	known risk	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases. Substrate for 3A4
Ibutilide	known risk	Females>Males
Imipramine	conditional risk	Risk of TdP in overdosage
Indapamide	possible risk	
Isradipine	possible risk	
Itraconazole	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Ketoconazole	conditional risk	Drug metabolism inhibitor
Levofloxacin	possible risk	
Levomethadyl	known risk	Not available in the U.S.
Lithium	possible risk	
Mesoridazine	known risk	
Methadone	known risk	Females>Males. Substrate for 3A4
Moexipril/HCTZ	possible risk	
Moxifloxacin	known risk	
Nicardipine	possible risk	
Nortriptyline	conditional risk	
Octreotide	possible risk	
Ofloxacin	possible risk	
Ondansetron	possible risk	
Oxytocin	possible risk	
Paliperidone	possible risk	
Paroxetine	conditional risk	
Pentamidine	known risk	Females > Males
Perflutren lipid microspheres	possible risk	
Pimozide	known risk	Females > Males. Substrate for 3A4
Probucol	known risk	No longer available in U.S.
Procainamide	known risk	
Protriptyline	conditional risk	
Quetiapine	possible risk	Substrate for 3A4
Quinidine	known risk	Females > Males. Substrate for 3A4
Ranolazine	possible risk	
Risperidone	possible risk	
Ritonavir	conditional risk	Substrate for 3A4
Roxithromycin*	possible risk	*not available in the United States
Sertindole	possible risk	
Sertraline	conditional risk	
Solifenacin	conditional risk	
Sotalol	known risk	Females > Males
Sparfloxacin	known risk	
Tacrolimus	possible risk	Substrate for 3A4
Telithromycin	possible risk	Substrate for 3A4

Table G: List of Potential QT Prolonging Drugs

Drug	QT risk*	Comment
Terfenadine	known risk	No longer available in U.S.Substrate for 3A4
Thioridazine	known risk	
Tizanidine	possible risk	
Trazodone	conditional risk	Substrate for 3A4
Trimethoprim-Sulfa	conditional risk	
Trimipramine	conditional risk	
Vandetanib	known risk	
Vardenafil	possible risk	Substrate for 3A4
Venlafaxine	possible risk	
Voriconazole	possible risk	
Ziprasidone	possible risk	

* Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT

Appendix 7. Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1

1.0 MEASURABILITY OF TUMOUR AT BASELINE

1.1 Definitions

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumour lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm);
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable);
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT

or MRI can be considered measurable lesions if the *soft tissue component* meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic mestastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new

lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials were recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers *alone* cannot be used to assess *objective* tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain).When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds of angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2.0 TUMOUR RESPONSE EVALUATION

2.1 Assessment of Overall Tumour Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above).

2.2 Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved, a *maximum* of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As previously noted, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm X 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as previously noted, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3 Response Criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

2.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms (CRFs) or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesion.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note*: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. If the radiologist is able to provide an actual measurement, that should be recorded, even if below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of Non-Target Lesion

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanations as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as previously noted, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large',

an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour. This is particularly important when the patient's baseline lesions show partial or complete response.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imagine can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. A 'positive' FDG-PET scan lesion is one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

   If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

   If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that time (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

2.4.1 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1- Time point response: patients with target (± non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	**CR**
CR	Non-CR/non-PD	No	**PR**
CR	Not evaluated	No	**PR**
PR	Non-PD or not all evaluated	No	**PR**
SD	Non-PD or not all evaluated	No	**SD**
Not all evaluated	Non-PD	No	**NE**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NE=inevaluable

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

2.4.3 Best Overall Response: All Time Points

The *best overall response* is determined once all the data for the patient is known.

Best response is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

2.4.4 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on the increase in size of the nodes. As noted earlier, this means that patients with CR may not have total sum of 'zero' on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesion), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Reference: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix 8. Child-Pugh Classification

CTP score is obtained by adding the score for each parameter in the table below.

CTP class: A = 5-6 points

B = 7-9 points

C = 10-15 points

Child Pugh Points			
Parameter	**1**	**2**	**3**
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
PR (sec prolonged) or INR	< 4 < 1.7	4-6 1.7 – 2.3	> 6 > 2.3

Appendix 9. Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Reference: Oken MM, Creech RH, Tormey DC, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Appendix 10. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study drug, whether or not considered related to the study drug. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
 	
• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible

suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 10.1.8.1. Also, "lack of efficacy" or "failure of expected pharmacological action" does not constitute an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).

10.3 Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study drug under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study drug under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

- **Assessment of Causality**

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- The Investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the Investigator does not know whether or not the study treatment caused the event, then the event will be handled as "related to study treatment" for reporting purposes, as defined by the Sponsor. In addition, if the Investigator determines that an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.4 Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

Appendix 11. Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Patients who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patients’s individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For patients with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the Sponsor.

The patient should return to the Investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (e.g., biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

Appendix 12. ECG Findings of Potential Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the Investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the Investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

Appendix 13. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 global pandemic and will become effective for other public emergencies only upon written notification from Pfizer.
Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

While SARSCoV-2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV-2. Patients with active infections are excluded from study participation as per exclusion criteria 16. When the infection resolves, the patient may be considered for re-screening.

13.1 Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study patients at scheduled visits per the Schedule of Activities (Section 8) or unscheduled visits. Telehealth visits may be used to continue to assess patient safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the patient and the Investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study treatment(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 10.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the patient is adhering to the contraception method(s) required in the protocol. Refer to Section 7.1.9 and Section 13.2.1 of this appendix regarding pregnancy tests.

Study patients must be reminded to promptly notify site staff about any change in their health status.

13.2 Alternative Facilities for Safety Assessments

13.2.1 Laboratory Testing

If a study patient is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Refer to Section 7.1.6 Clinical Safety Laboratory Assessments, Table 6 for the list of safety laboratory evaluations, including pregnancy testing required per protocol.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the patient's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a patient requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the patient to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the patient's source documents/medical records and relevant data recorded on the CRF. Confirm that the patient is adhering to the contraception method(s) required in the protocol.

13.2.2 Imaging

If the patient is unable to visit the study site for safety imaging assessments (e.g., CT, MRI, X-ray, ECHO or MUGA), the patient may visit an alternative facility to have the safety imaging assessments performed. Qualified study site personnel must order, receive, and review results.

13.2.3 Electrocardiograms

If the patient is unable to visit the study site for ECGs, the patient may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

13.2.4 Study Treatment

If the safety of a trial patient is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that patient from study treatment must be considered.

Study drugs may be shipped by courier to study patients if permitted by local regulations and in accordance with storage and transportation requirements for the study drugs. Pfizer does not permit the shipment of study drugs by mail. The tracking record of shipments and the

chain of custody of study drugs must be kept in the patient's source documents/medical records.
The following is recommended for the administration of study drugs for patients who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV-2 infection:

- For symptomatic patients with active SARS-CoV-2 infection, study drugs should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV-2 infection.
- Prior to restarting treatment, the patient should be afebrile for 72 hours, and SARS-CoV-2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described in protocol Section 5.4.2 for any concomitant medication administered for treatment of SARS-CoV-2 infection.

13.2.5 Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the patient's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Physical exam including dermatological lesions and vital signs
- Review and record study treatment(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 10.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the patient is adhering to the contraception method(s) required in the protocol. Refer to Section 7.1.9 and Section 13.2.1 of this appendix regarding pregnancy tests.

13.2.6 Adverse Events and Serious Adverse Events

If a patient has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical treatment provided. Temporary discontinuation of the study treatment may be medically appropriate until the patient has recovered from COVID-19.

It is recommended that the Investigator discuss temporary or permanent discontinuation of the study drug with the study medical monitor.