Title Page

A PHASE 1, RANDOMIZED, OPEN-LABEL STUDY IN HEALTHY PARTICIPANTS TO ESTIMATE THE BIOAVAILABILITY OF TWO NEW ENCORAFENIB FORMULATIONS RELATIVE TO THE CURRENT FORMULATION AND TO EVALUATE THE EFFECT OF A PROTON-PUMP INHIBITOR ON ENCORAFENIB PLASMA PHARMACOKINETICS

Study Intervention Number:	PF-07263896
Study Intervention Name:	Encorafenib
US IND Number:	111003
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Protocol Number:	C4221024
Phase:	1

Brief Title: A Phase 1 Relative Bioavailability Study Evaluating two new Encorafenib Formulations

Document History

Document	Version Date
Amendment 1	27 June 2022
Original protocol	05 May 2022

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs and any global protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 1 (27 June 2022)

Overall Rationale for the Amendment: In response to the COVID-19 pandemic, COVID-19 assessments were incorporated into the protocol template to minimize risk for participants and staff. PCRUs have now changed their COVID-19 procedures to not require testing and temperature checks at screening. This amendment is designed to update the protocol based on the new PCRU COVID-19 procedures.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Table 1 Periods 1, 2 and 3	COVID-19 test removed at screening	Updated to accommodate new COVID-19 Guidelines at the PCRU that no longer require COVID-19 testing at screening.	Substantial
Table 1 Periods 1, 2 and 3	Temperature check removed at screening	Updated to accommodate new COVID-19 Guidelines at the PCRU that no longer require a temperature check at screening.	Substantial
Section 5.2 Exclusion Criteria	Updated language to exclude participants with a positive COVID-19 test at first admission	Updated to accommodate new COVID-19 Guidelines at the PCRU that no longer require COVID-19 testing at screening.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 8.3.5 COVID-19 Specific Assessments	COVID-19 test removed at screening	Updated to accommodate new COVID-19 Guidelines at the PCRU that no longer require COVID-19 testing at screening.	Substantial
Section 5.3.2 Meals and Dietary Restrictions	Section was updated to align with exclusion criterion 6 on restrictions of food/drink that can be taken before encorafenib dosing.	Changed to correct protocol inconsistency.	Nonsubstantial
Section 6.1.1 Administration	Rabeprazole formulation was mistakenly noted as a capsule and was changed to a tablet.	Rabeprazole will be administered as a tablet at the PCRU.	Nonsubstantial
Table 1 Periods 1, 2 and 3	Reference updated	Table referenced the wrong section of the protocol.	Nonsubstantial
Section 9.5 Sample Size Determination	90% confidence intervals for AUC_{inf} and C_{max} were estimated based on 9 participants instead of 18.	Nine participants were required for the PPI drug-drug interaction of the study. However, the 90% CIs were calculated for 18 participants instead of 9 participants. Thus, the 90% CI data were updated based on 9 participants.	Nonsubstantial
Table 9 Confidence Interval Estimation of PK Endpoints for PPI Effect	90% confidence intervals for AUC_{inf} and C_{max} were estimated based on	Nine participants were required for the PPI drug-drug interaction of the study. However, in	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	9 participants instead of 18.	Table 9, the 90% CIs were calculated for 18 participants instead of 9 participants. Thus, the 90% CI data in Table 9 were updated based on 9 participants.	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Open-Label Study in Healthy Participants to Estimate the Bioavailability of two new Encorafenib Formulations Relative to the Current Formulation and to Evaluate the Effect of a Proton-Pump Inhibitor on Encorafenib Plasma Pharmacokinetics

Brief Title: A Phase 1 Relative Bioavailability Study Evaluating two new Encorafenib Formulations

Regulatory Agency Identification Number(s):

US IND Number:	111003
EudraCT Number:	N/A
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4221024
Phase:	1

Rationale

In order to decrease the size of the current formulated encorafenib capsule and improve the physical stability, 2 new encorafenib tablet formulations have been developed. This study is intended to select the optimal tablet formulation for commercialization based on the pharmacokinetics. In addition, the present dissolution data does not provide enough confidence to exclude the achlorhydric population (PPI effect) from the rBA study. Because of this difference, a preliminary assessment of the effect of a proton-pump inhibitor on the pharmacokinetics of the 2 encorafenib tablet formulations will also be conducted to assist in the formulation selection.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the relative BA of 2 new encorafenib 75-mg tablet formulations CCI to the commercially available encorafenib formulated capsule (CAP) administered under fasted conditions to adult healthy participants.	• Plasma AUC_{inf}, AUC_{last} and C_{max} for encorafenib (alone and with rabeprazole).
Secondary:	**Secondary:**
• To assess the safety and tolerability of the 3 formulations (CCI and CAP) encorafenib 75-mg, when given alone and in	• Overall safety profile as characterized by laboratory tests, vital signs, ECGs, and adverse events.

Objectives	Endpoints
combination with rabeprazole in adult healthy participants. • To estimate the effect of rabeprazole on the PK of [redacted].	• Other plasma PK parameters for encorafenib (alone and with rabeprazole): T_{max}, $t_{1/2}$, CL/F, and V_z/F, if possible.

Overall Design

This study will be an open-label, randomized, 4-period, 6-sequence study in adult healthy participants.

Number of Participants

A sufficient number of participants will be screened to ensure that at least 18 participants are enrolled in the study.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Participants must be male or female of non-childbearing potential of 18 years of age or older, inclusive, at the time of signing the ICD.

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

4. BMI of 17.5 to 30.5 kg/m^2; and a body weight >50 kg (110 lb).

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease. Evidence of any active and uncontrolled bacterial or viral infection.

2. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

3. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb or HCVAb. Hepatitis B vaccination is allowed.

4. Positive COVID-19 test at first admission.

5. Other medical or psychiatric conditions, laboratory test abnormalities, other conditions or situations related to COVID-19 pandemic or, in the investigator's judgment, make the participant inappropriate for the study.

6. Use of prescription or non-prescription medications within 7 days prior to the first dose of encorafenib with the exception of moderate/potent CYP3A inducers which are prohibited within 14 days plus 5 half-lives prior to the first dose.

7. History of known sensitivity to rabeprazole, substituted benzimidazoles or to any component of the rabeprazole formulation.

8. Previous administration with an investigational product (drug or vaccine) within 30 days.

9. Known hypersensitivity to encorafenib or its excipients.

10. A positive urine drug or cotinine test.

11. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest.

12. Baseline standard 12 lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results.

13. AST or ALT level ≥ 1.5 × ULN.

14. Total bilirubin level ≥1.5 × ULN.

15. Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2.

Study Arms and Duration

For Periods 1 through 3, participants will receive a single 75-mg encorafenib formulation during each period: CCI (Treatment A), CCI (Treatment B) and CAP (Treatment C) formulations, all under fasted conditions. In order to provide the most flexibility, the participants may remain in the PCRU from the time of admission on Day -1 of Period 1 until

discharge after the 48-hour PK collection in Period 4 based on the discretion of the investigator. There will be a minimum 5-day washout period between encorafenib doses in these periods. Serial PK samples will be collected prior to and after administration of each encorafenib dose.

During Period 4, in order to evaluate the effect of rabeprazole on the encorafenib PK for the 2 new tablet formulations, participants will receive either a single 75-mg dose of CCI (Treatment D) or CCI (Treatment E) following 5 days of 20 mg QD rabeprazole. The rabeprazole dosing in Period 4 must begin only after the 48-hour PK sample in Period 3 has been collected. Serial PK samples will be collected prior to and after encorafenib dosing.

The total duration of the study will be approximately 90 days including screening. Participants will be confined to the PCRU for a maximum of 21 days. Participants who withdraw from the study may be replaced at the discretion of the investigator and upon consultation with the sponsor.

Statistical Methods

Relative Bioavailability (Periods 1-3):

Natural log transformed encorafenib AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Treatment C (encorafenib CAP) is the Reference Treatment while Treatments A and B (CCI and CCI tablet formulations) are the Test Treatments. This analysis will include only data from Treatments A, B and C.

PPI effect (Period 4) :

Natural log transformed encorafenib AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. For the CCI tablet formulation, Treatment A (CCI tablet) is the Reference Treatment while Treatment D (CCI tablet administered with rabeprazole) is the Test Treatment (this analysis will only include data from Treatments A and D). For the CCI tablet formulation, Treatment B CCI tablet) is the Reference Treatment while Treatment E (CCI tablet administered with rabeprazole) is the Test Treatment (this analysis will only include data from Treatments B and E).

Ethical Considerations:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Participants may experience some adverse events.	Please see Section 2.2.4 for adverse event data of encorafenib in non-cancer participants. See the encorafenib IB for additional safety information.	All participants will be confined in the clinical sites with close monitoring and only be discharged once all AEs are stabilized. If necessary, a participant will be transferred to a facility with an appropriate level of care to achieve stabilization or until SAEs have resolved.
Study Intervention(s) Encorafenib, Rabeprazole		
Most common risks associated with encorafenib include headache, flushing/erythema, paresthesia, and feeling hot after a single dose.	The potential risks are based on AEs reported in previous clinical studies with encorafenib in healthy participants.	AEs, vital signs, ECGs, and clinical laboratory test results will be monitored on an ongoing basis. Instructions for managing potential cases of drug-induced liver injury, should they occur, are provided in Appendix 6.
Secondary skin neoplasms are known adverse effects of treatment with single-agent BRAF inhibitors including encorafenib.	Risk of developing secondary skin neoplasms is evident in the oncology treatment setting involving BRAF inhibitors including encorafenib. This adverse event was not reported with any of the other 5 clinical studies already conducted with healthy participants. Additionally, this event has not been observed after a single encorafenib dose in any patient studies either.	
Most common risks associated with rabeprazole include pain, pharyngitis, infection, flatulence, and constipation.	The potential risks are based on AEs reported in the USPI.	

Other		
Risk of COVID-19 contamination during study.	During the ongoing pandemic, healthy participants could be infected with SARS-COV-2 virus through study participation. This could lead to increased health risk for the participants and others in the study.	COVID-19 specific assessments will be conducted in this study according to Table 1 and Table 2.

Encorafenib single doses to be administered in this study are not expected to provide any clinical benefit to healthy participants.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA tables provide an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA tables, in order to conduct evaluations or assessments required to protect the well-being of the participant.

The scheduled activities are listed in Table 1 for Periods 1, 2 and 3 and in Table 2 for Period 4.

Table 1. Periods 1, 2 and 3

Visit Identifier Abbreviations used in this table may be found in Section 10.9.	**Screen**	**Period 1 to Period 3**					**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**		**Day 2**	**Day 3**		• All screening should be done ≤ 28 days before the first dose. • Study Day relative to start of study intervention (Day 1).
Hours After Dose			**0**	**2**	**24**	**48**		• Hour 0 = predose sample collection
Informed consent	X							• See Section 10.1.2 for additional information.
CRU confinement		X	→	→	→	→		• Participants may be discharged on Day 3 after PK sample collection is completed at the discretion of the investigator.
Inclusion/exclusion criteria	X	X						• Reviewed at screening and admission.
Medical/medication history	X	X						• Medical history: illegal drug, alcohol and tobacco use. • Medication history: prescription, non-prescription or supplements.
Physical examination (full)	X	X						• A full PE will only be performed either at screening or at admission during Period 1.
Safety laboratory tests	X	X					X	• Safety lab tests will be collected at screening, admission(s) and discharge, and at the discretion of the investigator. • See Section 10.2 for additional information on specific clinical laboratory tests.
Demography	X							

Table 1. Periods 1, 2 and 3

Visit Identifier Abbreviations used in this table may be found in Section 10.9.	**Screen**	**Period 1 to Period 3**					**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**		**Day 2**	**Day 3**		• All screening should be done ≤ 28 days before the first dose. • Study Day relative to start of study intervention (Day 1).
Hours After Dose			**0**	**2**	**24**	**48**		• Hour 0 = predose sample collection
Height and body weight	X							• See Section 8.3.1
Contraception check	X	X				X	X	• Contraception check on Day 3 if participant is discharged.
FSH	X							• See Section 10.4.3 for additional information.
Urine drug testing	X	X						• Cotinine test included. • If participants are confined to the PCRU between periods, Day -1 assessments not required. • See Section 10.2 for additional information.
12-Lead ECG	X		X	X			X	• See Section 8.3.3 for additional information. • Triplicate ECGs will be conducted pre-dose on Day 1. All other ECG measurements will be single ECGs.
Blood pressure and pulse rate	X		X	X			X	• See Section 8.3.2 for additional information.
HIV, HBsAg, HBcAb, HCVAb	X							• See Section 10.2 for additional information.
COVID-19 questionnaire	X	X						• Per local PCRU procedures.
COVID-19 PCR testing		X						• See Section 8.3.5 and Section 10.2 for additional information. • Per local PCRU procedures.
COVID-19 check temperature		X						• Per local PCRU procedures.
Encorafenib administration			X					• See Section 6.1.1 for additional information.
Pharmacokinetic blood sampling for encorafenib			X	→	→	→	X	• Refer to Table 3 and Section 8.5 for additional information.

Table 1. Periods 1, 2 and 3

Visit Identifier Abbreviations used in this table may be found in Section 10.9.	**Screen**	**Period 1 to Period 3**					**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**		**Day 2**	**Day 3**		• All screening should be done ≤ 28 days before the first dose. • Study Day relative to start of study intervention (Day 1).
Hours After Dose			**0**	**2**	**24**	**48**		• Hour 0 = predose sample collection
Retained Research Sample for Genetics (Prep D1)			X (Period 1 only)					• Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. See Section 8.6.2.
Concomitant treatment(s)	X	X	X	→	→	→	X	• See Section 6.9 for additional information.
Serious and nonserious AE monitoring	X	X	X	→	→	→	X	• See Section 8.4.3 for follow-up AE and SAE assessments.

Table 2. Period 4

Visit Identifier Abbreviations used in this table may be found in Section 10.9.	**Period 4**						**F/U**	**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -5**	**Day -4 to Day -1**	**Day 1**		**Day 2**	**Day 3**	**29-35 Days**		• Day relative to start of study intervention (Day 1). • Follow-up may occur via telephone. Contact and must occur 29 to 35 days after administration of the final dose of study intervention
Hours After Dose			**0**	**2**	**24**	**48**			• Hour 0 = predose sample collection
CRU confinement	X	→	→	→	→	X			
Safety laboratory tests						X		X	• See Section 10.2 for additional information on specific clinical laboratory tests.
Contraception check							X	X	• See Section 10.4 for additional information.
12-Lead ECG			X	X				X	• See Section 8.3.3 for additional information. • Triplicate ECGs will be conducted pre-dose on Day 1. All other ECG measurements will be single ECGs.
Blood pressure and pulse rate			X	X				X	• See Section 8.3.2 for additional information.
Rabeprazole administration	X	X							• See Section 6.1.1 for additional information.
Encorafenib administration			X						• See Section 6.1.1 for additional information.
Pharmacokinetic blood sampling for encorafenib			X	→	→	→		X	• Refer to Table 3 and Section 8.5 for additional information.
CRU discharge						X			
Concomitant treatment(s)	X	X	X	→	→	→	X	X	• See Section 6.9 for additional information.
Serious and nonserious AE monitoring	X	X	X	→	→	→	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.

Table 3. Pharmacokinetic Assessments

																Notes
Study Day	**1**													**2**	**3**	Day relative to start of study intervention (Day 1).
Hours Before/After Dose	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**6**	**8**	**10**	**12**	**24**	**48**	Hour 0 = predose sample collection
Encorafenib administration	X															
Encorafenib PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

2. INTRODUCTION

Encorafenib is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test, or in combination with cetuximab, for the treatment of patients with mCRC with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

2.1. Study Rationale

Formulated drug product containing encorafenib is currently available as a 75-mg size double zero capsule for commercial uses. At the approved dose for metastatic melanoma (450 mg QD), patients are required to swallow 6 capsules each day within a short period of time. The capsule burden and challenge for many patients to consistently ingest six double-zero capsules has been noted during clinical development and subsequently post-commercialization. Patients have often requested the option to open the capsules because they are too large to swallow. Additionally, there is an effort to improve the physical stability of encorafenib for primary packaging flexibility. Therefore, there is a need for a formulation that is smaller in size with improved stability; this is the basis for evaluation of the BA of the alternate formulation relative to the CAP for future commercial use.

Alternative formulations have been developed as IR tablets, to deliver the 75-mg dose in a 10mm standard round tablet, improve physical stability, and are intended to provide an alternative dosage form to be used for all patients, especially those who have difficulty in swallowing the commercial capsules.

Two encorafenib tablet formulations are being evaluated in this clinical study. Both novel formulations contain the same HME composition which contains encorafenib within an amorphous solid dispersion. The formulations differ in the extragranular excipients chosen to compress the tablet cores. Specifically, the formulation designated as CCI contains only CCI as the extragranular diluent and the formulation designated as CCI contains CCI as the extragranular diluents. These 2 tablet formulations are differentiated in terms of dissolution release profile and the clinical evaluation of both tablet core compositions will provide elucidation of formulation design space which can be used to inform future commercial formulation design strategies for encorafenib. For clarity, details regarding the 2 tablet formulations are provided in Table 4.

Table 4. Summary of the Two New Tablet Formulations

Name and Description	Tablet Abbreviation	Description
CCI	CCI	Immediate-release tablet formulated with CCI as the single extragranular diluent
CCI	CCI	Immediate-release tablet formulated with both CCI and CCI as extragranular diluents

This study is intended to select the optimal tablet formulation for commercialization based on the PK. In addition, a preliminary assessment of the effect of a PPI on the PK of the 2 encorafenib tablet formulations will also be conducted to assist in the formulation selection.

2.2. Background

Encorafenib is a novel oral small-molecule kinase inhibitor, which suppresses the RAF/MEK/ERK pathway in tumor cells expressing the BRAF V600E mutation. Similar to other selective small molecule RAF kinase inhibitors, encorafenib inhibits COT and RAF-1 (CRAF), BRAF, as well as BRAF V600E in cell-free assays. However, this class of inhibitor does not inhibit RAF/MEK/ERK signaling in cells expressing wild-type BRAF. In the human melanoma cell line A375 (BRAF V600E), encorafenib potently inhibits phospho-MEK, phosphor-ERK and proliferation, resulting in cell cycle arrest and apoptosis. Given the high degree of selectivity against other kinases, encorafenib has no antiproliferative activity in tumor cell lines that express wild-type BRAF and is highly selective for BRAF V600E/D/K containing cell lines, with the greatest sensitivity observed in $BRAF^{mt}$ melanoma and CRC lineages. Encorafenib has been clinically evaluated in the oncology setting as a single agent and in combination with other targeted agents, as well as in healthy subjects for bioavailability, human ADME, food effect, hepatic impairment and DDIs.

2.2.1. Nonclinical Pharmacology

Encorafenib is a highly selective ATP-competitive small-molecule RAF kinase inhibitor which suppresses the RAF/MEK/ERK pathway in tumor cells expressing BRAFV600E. For example, the half-maximal response concentration (EC50) for suppression of pMEK and 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 EC50 = 4 nM. Similar to other selective small-molecule RAF kinase inhibitors, encorafenib inhibits CRAF, BRAF, as well as BRAF V600E 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.

Encorafenib's predominant circulating metabolite, 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 ADME study. The results showed activities of > 50% inhibition at 10 μM were found on kinase insert domain receptor (half-maximal inhibitory concentration [IC50] = 1.8 μM, n = 1) and PDE4D (IC50 = 4.2 μM, n = 2), showing significantly less potency than encorafenib. LHY746 was also evaluated in in vitro activity studies and confirmed to be inactive with respect to inhibiting melanoma cell proliferation.

For more detailed information, refer to the current encorafenib IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Encorafenib is a substrate of P-gp and is associated 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 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 humans than in other species. Encorafenib is metabolized by 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).

In vitro experiments indicate that encorafenib is a relatively potent reversible inhibitor of uridine 5'-diphospho-glucuronosyltransferase-glucuronosyltransferase (UGT) 1A1, 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 BCRP, and a potent inhibitor of renal transporters OCT 2, OAT 1, OAT3 and hepatic transporters OCT1, OATP1B1 and OATP1B3. For more detailed information, refer to the current encorafenib IB.

2.2.3. Nonclinical Safety

Preclinical safety pharmacology data do not indicate a clinical risk for QTc prolongation, or adverse effects on the CNS or respiratory system for encorafenib or its primary metabolite, LHY746.

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.

For more detailed information, refer to the current encorafenib IB.

2.2.4. Clinical Overview

As of the data cutoff date of 11 May 2020, a total of 2117 healthy subjects and patients have received at least 1 dose of encorafenib, either as a single agent or in combination with other targeted agents. These patients constitute the encorafenib safety population, which includes 97 healthy subjects, 7 subjects with hepatic impairment and 2013 patients with advanced cancer (410 patients who received single-agent encorafenib and 1614 patients who received encorafenib combination therapy, with 11 patients who received both single-agent encorafenib and encorafenib + binimetinib combination therapy and 4 patients who received encorafenib + binimetinib combination therapy in 2 different studies). Based on the

experience from these studies, encorafenib has demonstrated an acceptable and manageable safety profile.

Rabeprazole will be used in Period 4 of this study for assessment of the potential effect of a PPI on the PK of the HME formulations ([CCI] and [CCI] Rabeprazole is a commonly used PPI able to reduce gastric acid. The approved dose for delayed release rabeprazole (for gastroesophageal reflux disease) is 20-mg QD.

The first generation encorafenib capsule was previously studied with rabeprazole 20-mg in a Phase 1, open-label, 2-arm, parallel-group, fixed-sequence study. The results show that co-administration of 100-mg encorafenib with rabeprazole had no overall effect on the extent of exposure and peak exposure to encorafenib, when 100-mg encorafenib was co-administered with multiple oral once-daily doses of 20-mg rabeprazole, relative to when 100-mg encorafenib was administered alone. The administration of a single 100 mg oral dose of encorafenib in the presence of multiple oral doses of 20-mg rabeprazole was safe (as evidenced by the absence of Grade 3/severe, Grade 4/life-threatening, and Grade 5/death as well as the absence of subject discontinuation deemed necessary by the Investigator due to AEs). In Period 4 of this study, 20 mg rabeprazole QD will be administered for 5 days to explore the potential effect of a PPI on PK of both new tablet formulations.

For detailed clinical information, refer to the current encorafenib IB. For additional information regarding rabeprazole, please refer to the current rabeprazole USPI.

2.3. Benefit/Risk Assessment

Encorafenib is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data for further clinical development of new tablet formulation and to inform the critical formulation compositional design parameters for commercial formulation development for encorafenib.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of encorafenib may be found in the current encorafenib IB which is the SRSD for this study.

Information about the known and expected benefits and risks and reasonably expected AEs of rabeprazole may be found in the rabeprazole USPI.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Participants may experience some adverse events.	Please see Section 2.2.4 for adverse event data of encorafenib in non-cancer participants. See the encorafenib IB for additional safety information.	All participants will be confined in the clinical sites with close monitoring and only be discharged once all AEs are stabilized. If necessary, a participant will be transferred to a facility with an appropriate level of care to achieve stabilization or until SAEs have resolved.
Study Intervention(s) Encorafenib, Rabeprazole		
Most common risks associated with encorafenib include headache, flushing/erythema, paresthesia, and feeling hot after a single dose.	The potential risks are based on AEs reported in previous clinical studies with encorafenib in healthy participants.	AEs, vital signs, ECGs, and clinical laboratory test results will be monitored on an ongoing basis. Instructions for managing potential cases of drug-induced liver injury, should they occur, are provided in Appendix 6.
Secondary skin neoplasms are known adverse effects of treatment with single-agent BRAF inhibitors including encorafenib.	Risk of developing secondary skin neoplasms is evident in the oncology treatment setting involving BRAF inhibitors including encorafenib. This adverse event was not reported with any of the other 5 clinical studies already conducted with healthy participants. Additionally, this event has not been observed after a single encorafenib dose in any patient studies either.	
Most common risks associated with rabeprazole include pain, pharyngitis, infection, flatulence, and constipation.	The potential risks are based on AEs reported in the USPI.	
Other		
Risk of COVID-19 contamination during study.	During the ongoing pandemic, healthy participants could be infected with SARS-COV-2 virus through study participation. This could lead to increased health risk for the participants and others in the study.	COVID-19 specific assessments will be conducted in this study according to Table 1 and Table 2.

2.3.2. Benefit Assessment

No clinical benefit is expected for participants enrolled in this study, but the results from this study are intended to develop and eventually commercialize a new encorafenib formulation to extend the use of encorafenib in patients who have trouble swallowing the capsule formulation currently on the market.

2.3.3. Overall Benefit/Risk Conclusion

Encorafenib single doses to be administered in this study are not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate PK data for evaluation of a new encorafenib formulation. Single oral doses of 50-mg and 100-mg encorafenib have been safely administered previously to approximately 90 healthy participants in 5 healthy participant clinical studies.

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of encorafenib may be found in the current encorafenib IB, which is the SRSD for this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the relative BA of 2 new encorafenib 75-mg tablet formulations (CCI and CCI to the commercially available encorafenib formulated capsule (CAP) administered under fasted conditions to adult healthy participants.	• Plasma AUC_{inf}, AUC_{last} and C_{max} for encorafenib (alone and with rabeprazole).
Secondary:	**Secondary:**
• To assess the safety and tolerability of the 3 formulations (CCI and CAP) encorafenib 75-mg, when given alone and in combination with rabeprazole in adult healthy participants. • To estimate the effect of rabeprazole on the PK of CCI and CCI	• Overall safety profile as characterized by laboratory tests, vital signs, ECGs, and adverse events. • Other plasma PK parameters for encorafenib (alone and with rabeprazole): T_{max}, $t_{1/2}$, CL/F, and V_z/F, if possible.

4. STUDY DESIGN

4.1. Overall Design

This study will be an open-label, randomized, 4-period, 6-sequence study in adult healthy participants.

Periods 1 through 3 will estimate the relative bioavailability of the 2 new encorafenib tablet formulations (CCI and CCI compared to the commercially available CAP formulation using a 75-mg encorafenib single dose administered under fasted condition. Period 4 will explore the potential effect of a PPI (rabeprazole) on the PK of encorafenib administered as

the CCI and CCI tablet formulations. Participants will receive either the CCI or CCI formulation with rabeprazole in Period 4.

Participants will be randomized into 1 of 6 treatment sequences as outlined in Table 5.

For Periods 1 through 3, participants will receive a single 75-mg encorafenib formulation during each period: CCI (Treatment A), CCI (Treatment B) and CAP (Treatment C) formulations, all under fasted conditions. In order to provide the most flexibility, the participants may remain in the PCRU from the time of admission on Day -1 of Period 1 until discharge after the 48-hour PK collection in Period 4 based on the discretion of the investigator. There will be a minimum 5-day washout period between encorafenib doses in these periods. Serial PK samples will be collected prior to and after administration of each encorafenib dose.

During Period 4, in order to evaluate the effect of rabeprazole on the encorafenib PK for the 2 new tablet formulations, participants will receive either a single 75-mg dose of CCI (Treatment D) or CCI (Treatment E) following 5 days of 20 mg QD rabeprazole. The rabeprazole dosing in Period 4 must begin only after the 48-hour PK sample in Period 3 has been collected. Serial PK samples will be collected prior to and after encorafenib dosing.

Approximately 18 participants will be enrolled into the study. Each participant will receive 4 single 75-mg doses of encorafenib during Periods 1 through 4, and in addition, 20-mg rabeprazole QD for 5 days in Period 4.

The total duration of the study will be approximately 90 days including screening. Participants will be confined to the PCRU for a maximum of 21 days. Participants who withdraw from the study may be replaced at the discretion of the investigator and upon consultation with the sponsor.

Table 5. Trial Design

Treatment Sequence	Period 1	Washout	Period 2	Washout	Period 3	Washout	Period 4
1 (N=3)	A	At least 5 day washout[a]	B	At least 5 day washout[a]	C	At least 5 day washout[a]	D
2 (N=3)	A		C		B		E
3 (N=3)	B		C		A		D
4 (N=3)	B		A		C		E
5 (N=3)	C		A		B		D
6 (N=3)	C		B		A		E

a.between successive encorafenib doses

Treatments:

- Treatment A (Test 1 for BA evaluation, Reference 1 for PPI effect): A single 75 mg encorafenib dose as the CCI formulation will be administered on the morning of Day 1 after an overnight fast of at least 10 hours.

- Treatment B (Test 2 for BA evaluation, Reference 2 PPI effect): A single 75 mg encorafenib dose as the CCI formulation will be administered on the morning of Day 1 after an overnight fast of at least 10 hours.
- Treatment C (Reference for BA evaluation): A single 75 mg encorafenib dose as CAP formulation will be administered on the morning of Day 1 after an overnight fast of at least 10 hours.
- Treatment D (Test 1 for PPI evaluation): 20 mg rabeprazole will be administered approximately 1 hour prior to dinner on Day -5 through Day -1. A single 75 mg encorafenib dose as CCI formulation will be administered on the morning of Day 1 after an overnight fast of at least 10 hours.
- Treatment E (Test 2 for PPI evaluation): 20 mg rabeprazole will be administered approximately 1 hour prior to dinner on Day -5 through Day -1. A single 75 mg encorafenib dose as CCI formulation will be administered on the morning of Day 1 after an overnight fast of at least 10 hours.

4.2. Scientific Rationale for Study Design

Single doses of encorafenib up to 100-mg have been safely administered to about 90 healthy participants in 5 clinical studies ensuring little risk to healthy adult participants in the current study (Section 2.2).

Genetic Toxicity: The GLP Ames and chromosomal aberration assays as well as a rat micronucleus study indicate that encorafenib is not genotoxic.

Washout period: The mean elimination half-life after a single dose of encorafenib is approximately 3.5 hours. Thus, a 18-hour washout period (~5 half-lives) is considered adequate for the washout of the encorafenib from plasma. During the study, plasma concentrations should typically have dropped to BLQ before administration of the next dose (ie, no residual concentrations from the prior period) to minimize the carryover from the previous treatment. Based on previous clinical experience with encorafenib, a 5-day washout period is considered sufficient for plasma encorafenib concentrations to return to BLQ after administration of a single dose. Therefore, in this study, a 5-day washout period has been selected between successive encorafenib doses for periods with PK collections.

Rationale for Inclusion of PPI Assessment: Encorafenib being a weak base would require inclusion of achlorhydric subjects to assess the effect of a PPI on the PK, unless a non-significant difference (≤15%) between the dissolution profiles of first generation capsules and second generation tablets is demonstrated in a medium with pH 3.0–6.8.[1,2,3] Selection of the exact medium within this pH range has proven to be complex due to various factors. Considering this, the present dissolution data does not provide enough confidence to exclude the achlorhydric population (PPI effect) from the rBA study. Because of this difference, both new tablet formulations will also be tested for clinically significant pH dependent interactions.

Study Treatment Rationale for Rabeprazole: PPIs are a group of drugs that have strong inhibitory effects on acid secretion in the stomach through suppression of the gastric proton pump (H, K-ATPase). PPIs exert their effect by increasing gastric pH and are the very

important treatment options for acid-related diseases. All PPIs showed inhibitory effect on CYP2C9, 2C19, and 3A4 to some extent. Among those PPIs, rabeprazole showed the lowest inhibitory potency compared to other PPIs.[4,5] In addition, rabeprazole is predominantly converted to a thioether metabolite by non-enzymatic reduction and metabolism by CYP enzymes is only the minor elimination pathway. Therefore, the impact of enzyme polymorphism (such as CYP2C19) would be the lowest for rabeprazole among all PPIs.[6,7] Meta-analysis of multiple studies shows that rabeprazole has relatively high antisecretory potency among PPIs tested.[6] Since acid control by PPIs is a sustained effect, PPIs are commonly given daily despite the short elimination half-life (about 2 hours or less).[7] Since encorafenib is partially metabolized by CYP2C19 there is a potential that rabeprazole may increase encorafenib plasma concentrations due to its CYP2C19 inhibitory effect, to minimize potential drug interaction between rabeprazole and encorafenib, in this study, rabeprazole as 20-mg will be administered in the evening from Day -1 to Day -5, and 75-mg encorafenib will be administered in the morning on Day 1 for the evaluation of any potential effect of PPI on the PK of encorafenib. With the short half-life of rabeprazole, there will be minimal systemic exposure of rabeprazole at the time of rabeprazole administration in the current design.

4.2.1. Choice of Contraception/Barrier Requirements

Nonclinical studies suggest risk for severe manifestations of developmental toxicity at relevant clinical exposures for encorafenib. Therefore, the use of a highly effective method of contraception is required for male participants and their female partners of childbearing potential (see Appendix 4). Only female participants on non-childbearing status will be enrolled.

4.2.2. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

4.3.1. Encorafenib Dose Rationale

The approved dose of encorafenib for the treatment of metastatic melanoma is 450-mg QD (administered as six 75-mg capsules, in combination with binimetinib) and 300-mg QD (administered as four 75-mg capsules, in combination with cetuximab) for mCRC. In clinical study CLGX818X2101, the MTD for encorafenib was determined to be 450-mg QD and encorafenib has demonstrated dose proportional PK from 50 to 700-mg following single-dose administration in patients. Single 50-mg and 100-mg doses of encorafenib have been administered to approximately 90 adult healthy participants in 5 clinical studies and were well-tolerated and without any reported SAEs.

Based on the safety data of encorafenib and prior clinical experience as described above, a single 75-mg dose, with a 5 day washout between successive encorafenib doses, for 4 periods, is expected to pose little risk to healthy adult participants.

4.3.2. Rabeprazole Drug Selection and Dose Rationale

Rabeprazole is primarily dosed at 20-mg QD for many of its most common indications (healing of erosive or ulcerative GERD, treatment of symptomatic GERD in adults). Additionally, the findings from 2 clinical studies[8,9] indicate that the rabeprazole dosing regimen utilized in this protocol will ensure an intragastric pH>4, thus allowing the evaluation of the maximum effect of gastric acid suppression on encorafenib pharmacokinetics.

4.4. End of Study Definition

The end of the study will be defined as the date of last scheduled procedure shown in Table 2 for the last participant in the trial.

A participant will be considered to have completed the study if they have completed all periods of the study, including the last scheduled procedure shown in Table 1 and Table 2.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Participants must be male or female of non-childbearing potential (as defined in Appendix 4, Section 10.4.3) of 18 years of age or older, inclusive, at the time of signing the ICD.

   Refer to Appendix 4 for reproductive criteria for male Section 10.4.1 and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Body Weight:

4. BMI of 17.5 to 30.5 kg/m^2; and a body weight >50 kg (110 lb).

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular (including history of prolonged QT syndrome), hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing). Evidence of any active and uncontrolled bacterial or viral infection.

2. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

3. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb or HCVAb. Hepatitis B vaccination is allowed.

4. Positive COVID-19 test at first admission.

5. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory test abnormality or other conditions or situations related to COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

6. Use of prescription or non-prescription medications, including vitamins, herbal and dietary supplements, grapefruit/grapefruit containing products, and Seville orange/Seville orange containing products within 7 days prior to the first dose of encorafenib with the exception of moderate/potent CYP3A inducers which are prohibited within 14 days plus 5 half-lives prior to the first dose of encorafenib. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

7. History of known sensitivity to rabeprazole, substituted benzimidazoles or to any component of the rabeprazole formulation. (Refer to rabeprazole USPI for additional warnings and precautions related to rabeprazole).

Prior/Concurrent Clinical Study Experience:

8. Previous administration with an investigational product (drug or vaccine) within 30 days.

9. Known hypersensitivity to encorafenib or its excipients.

Diagnostic Assessments:

10. A positive urine drug or cotinine test.

11. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

12. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms (or a history of prolonged QT syndrome), complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms and or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF and/or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

13. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST **or** ALT level ≥1.5 × ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.
    - Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (See for Section 10.7.2 calculation method).

Other Exclusion Criteria:

14. Male participants who are unwilling or unable to comply with the contraception requirement listed in Section 10.4.1.

15. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).

16. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

17. History of sensitivity to heparin or heparin-induced thrombocytopenia.

18. Participants who currently smoke or use other nicotine products (e.g. chewing tobacco, E-cigarettes).

19. Unwilling or unable to comply with the criteria in the Section 5.3 Lifestyle Considerations section of this protocol.

20. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that male participants are utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. It must be confirmed that female participants meet the criteria for non-childbearing potential. At time points indicated in SoA tables (Table 1 and Table 2), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample on Day 1 of each period. Participants must also abstain from all food and drink (except water) at least 4 hours post encorafenib dose on Day 1 of each period.

- Breakfast will not be provided on Day 1 of each treatment period.

- Water will be permitted until 1 hour prior to encorafenib administration on Day 1 in each period. There will be no water restrictions for rabeprazole dosing. Water may be consumed without restriction beginning 1 hour after dosing on Day 1 of each period. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 to 5 hours after encorafenib dosing on Day 1 of all periods

- Dinner will be provided approximately 9 to 10 hours after encorafenib dosing on Day 1 of all periods.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit -related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of encorafenib until collection of the final PK blood sample on the study.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of encorafenib dosing on Day 1 until collection of the final PK sample of each treatment period.

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at any time at the discretion of the investigator.

- Participants who currently smoke will not be enrolled in this study.

5.3.4. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after encorafenib dosing on Day 1 of each treatment period

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (ie, screen failures) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

Additionally during screening:

- For eligibility purposes, vital signs, laboratory tests, or ECG results may be repeated if an abnormal result is observed at the initial reading;

- In the event that the participation of a participant in the study is delayed and any required screening procedures will be outside of the allowed screening window (28 days), these screening procedures can be repeated;

- Participants who are not eligible based on a reversible medical condition or mild/acute/intercurrent illness may be re-evaluated after further testing/examination or re-screened after the condition has resolved.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Study interventions administered in this study will be encorafenib and rabeprazole.

Table 6. Summary of Encorafenib Formulations

Treatment References[a]	Protocol C4221024 Abbreviation	Route of Administration	DMID Description	CCI
Treatment A Treatment D	CCI	Oral	CCI	CCI
Treatment B Treatment E	CCI	Oral	CCI	CCI
Treatment C	CAP	Oral	Encorafenib 75 mg Size 00 white/flesh hard gelatin capsule	CCI

a. Treatment descriptions outlined in Section 4.1.

Encorafenib 75 mg tablets and capsules will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Delayed release 20 mg rabeprazole will be supplied by the CRU.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive encorafenib at approximately 0800 hours (plus or minus 2 hours) on Day 1 of each period. The investigator site personnel will administer encorafenib capsule/tablet during each period with approximately 240 mL of ambient temperature water. Participants will swallow the capsule/tablet whole, and will not manipulate or chew the capsule/tablet prior to swallowing.

During Period 4, the investigator site personnel will administer a 20 mg rabeprazole tablet with approximately 240 mL of ambient temperature water without food approximately 1 hour prior to the dinner on Day -5 to Day -1. Participants will swallow rabeprazole tablet whole and will not manipulate or chew the tablet prior to swallowing.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for ECG measurements), eating, and drinking beverages other than water during the first 4 hours after encorafenib dosing.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IP manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery*:* as described in the IPM.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider,

participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Encorafenib tablets and capsules will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets and capsules will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

The handling of rabeprazole should be according to the product package insert.

6.3. Assignment to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled. The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Blinding

This will be an open label study.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

No dose modifications, dosing interruptions, or dosing delays will be allowed in this healthy participant study.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation.

6.8. Treatment of Overdose

For this study, any dose of encorafenib greater than 75 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory test abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days prior to the first dose of encorafenib with the exception of moderate/potent CYP3A inducers which are prohibited within 14 days plus 5 half-lives prior to the first dose of encorafenib. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

During the study, acetaminophen (up to 1 g per 24-hour period) and ibuprofen (up to 800 mg per 24 hour period) may be administered at the discretion of the PI.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of either study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

If study intervention is permanently discontinued, the participant will not remain in the study for further evaluation. See the SoA tables for data to be collected at the time of discontinuation of study intervention.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA tables for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an AE or SAE, the AE or SAE must be recorded on the case report form (CRF) and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention 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 participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants 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 intervention 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 participant 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.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA tables. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA tables, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory test results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory test results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may be used without repeat collection, as appropriate.

Every effort should be made to ensure that protocol -required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol -required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study will be approximately 230 mL. The actual collection times of blood sampling may change; the time of actual collection will be recorded. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Prior and Concomitant Therapy sections of the protocol.

8.2. Efficacy Assessments

Efficacy assessments will not be applicable to this study

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA tables. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

A full physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and body weight will also be measured and recorded as per Table 1. For measuring body weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mmHg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected before dose administration on Day 1 of each period will serve as each participant's baseline QTcF value.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements (the last measurement prior to encorafenib dose in the first period). Additional ECG monitoring will occur if a) a postdose QTcF is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QTcF value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. Clinical Safety Laboratory Test Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 28 calendar days after the last dose of study intervention

should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.5. COVID-19 Specific Assessments

Participants will be tested for SARS-COVID-19 infection by PCR testing prior to being admitted to the clinic for confinement (Day -1 of Period 1) and a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 × 24 hours of CRU confinement), or if they develop COVID-19 like symptoms.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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 participant to discontinue the study intervention *(*see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant 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.

8.4.1. 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 participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues 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 participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant 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 participant permanently discontinues or temporarily discontinues study intervention 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 information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 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 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, 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 participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.4.2. 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 3.

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

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant 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 participant is lost to follow-up (as defined in Section 7.3).

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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4. 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 toward the safety of participants and the safety of a study intervention 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 intervention 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.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental

exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion or skin contact 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 participant or a participant'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 intervention and until 7 days 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 participant 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 should be reported as an SAE;

- 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 intervention.

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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion or skin contact.

The investigator must report EDB 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 EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant 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 EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

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

8.4.6. Cardiovascular and Death Events

Not Applicable.

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

Not Applicable.

8.4.8. Adverse Events of Special Interest

Not Applicable.

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in this study population.

8.4.9. Medical Device Deficiencies

Not Applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

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

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

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

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

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of Encorafenib

Blood samples of approximately 3 mL will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) or tripotassium ethylenediaminetetraacetic acid (K_3EDTA) for measurement of plasma concentrations of encorafenib as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will

not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of encorafenib. CCI [redacted].

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of encorafenib will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.5.2. Derivation of Pharmacokinetic Parameters

PK parameters, as appropriate, will be derived from the encorafenib concentration-time profiles as described in Table 7.

Table 7. Definitions of PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear-log trapezoidal method.
AUC_{inf} [a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$. where C_{last} is the predicted plasma concentration at the last quantifiable time point and kel is the elimination rate constant estimated from the log-linear regression analysis.
C_{max}	Maximum plasma concentration	Observed directly from the data.
T_{max}	Time for C_{max}	Observed directly from the data as time of first occurrence.
$t_{1/2}$ [a]	Terminal plasma elimination half-life	$Log_e(2)/k_{el}$ Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F[a]	Apparent clearance after oral dose	$Dose/AUC_{inf}$ after oral dose.

Table 7. Definitions of PK Parameters

Parameter	Definition	Method of Determination
V_z/F^a	Apparent volume of distribution after oral dose	Dose/(AUC_{inf}*k_{el}) after oral dose.
T_{last}	The time for C_{last}	Observed directly from the data

a. As data permits

Actual PK sampling times will be used in the derivation of PK parameters whenever possible. In the case that actual PK sampling times are not available, nominal PK sampling time may be used in the derivation of PK parameters.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA tables, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in laboratory manual and supporting documentation.

8.7. Biomarkers

Biomarkers will not be evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments will not be included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the Statistical Analysis Plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where

appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

No statistical hypothesis will be tested in this study.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Safety analysis set	All participants randomly assigned to a treatment sequence and who take at least 1 dose of encorafenib. Participants will be analyzed according to the formulation they actually received.
PK Concentration Analysis Set	The PK concentration population is defined as all participants randomized and treated who have at least 1 encorafenib concentration in at least 1 period.
PK Parameter Analysis Set	The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the encorafenib plasma PK parameters of primary interest in at least 1 treatment period.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. Pharmacokinetic Analyses

Encorafenib PK parameters following a single dose administration will be derived from the encorafenib plasma concentration versus time profiles using non-compartmental methods as data permit. The PK parameters to be assessed in this study, their definition, and method of determination are outlined in Table 6. Encorafenib PK parameters (AUC_{inf}, AUC_{last}, C_{max}, T_{max}, $t_{1/2}$, CL/F, and V_z/F) will be summarized descriptively by treatment. Individual participant parameters for AUC_{inf}, $AUC_{last\ and}$ C_{max} will be plotted by treatment and overlaid

with geometric mean. Similar presentations will also be made for other PK parameters, if considered relevant. Encorafenib concentrations will be listed and summarized descriptively by PK sampling time and treatment. Summary profiles (means and medians) of concentration time data will be plotted by treatment on linear and semi log scale. Individual participant concentration time profiles will be also presented. For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

Relative Bioavailability (Periods 1-3):

Natural log transformed encorafenib AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Treatment C (encorafenib CAP) is the Reference Treatment while Treatments A and B (CCI and CCI tablet formulations) are the Test Treatments. This analysis will include only data from Treatments A, B and C.

PPI effect (Period 4) :

Natural log transformed encorafenib AUC_{inf} (if data permit), AUC_{last} and C_{max} will be analyzed using ANOVA with treatment and sequence as a fixed effect and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. For the CCI tablet formulation, Treatment A (CCI tablet) is the Reference Treatment while Treatment D (CCI tablet administered with rabeprazole) is the Test Treatment (this analysis will only include data from Treatments A and D). For the CCI tablet formulation, Treatment B (CCI tablet) is the Reference Treatment while Treatment E (CCI tablet administered with rabeprazole) is the Test Treatment (this analysis will only include data from Treatments B and E).

9.3.2. Other Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BPs, pulse rates, and safety laboratory test data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported,

unless otherwise noted. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory test data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.3. Other Analyses

9.3.3.1. Retained Research Sample Analyses

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

No interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, and/or supporting clinical development.

9.5. Sample Size Determination

A sufficient number of participants will be screened to ensure that at least 18 participants are enrolled in the study.

The sample size is empirically selected and is not based on statistical power calculation.

For the comparison of the 2 new encorafenib tablet formulations to the commercially available CAP, a sample size of 18 PK evaluable participants will provide 90% CIs for the difference between treatments of ±0.1213 and ±0.1343 on the natural log scale for AUC_{inf} and C_{max}, respectively, with 80% coverage probability. Table 8 presents the width of 90% CI for different estimated effects.

Table 8. Confidence Interval Estimation of PK Endpoints for Bioavailability

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
AUC_{inf}	50%	0.4429, 0.5645	0.1216
	70%	0.6200, 0.7903	0.1703
	80%	0.7086, 0.9032	0.1946
	90%	0.7972, 1.0161	0.2189
	100%	0.8857, 1.1290	0.2433
	110%	0.9743, 1.2419	0.2676
	120%	1.0629, 1.3548	0.2919
	130%	1.1515, 1.4677	0.3162
	150%	1.3286, 1.6935	0.3649
C_{max}	50%	0.4371, 0.5719	0.1347
	70%	0.6120, 0.8006	0.1886
	80%	0.6994, 0.9150	0.2156
	90%	0.7869, 1.0294	0.2425

Table 8. Confidence Interval Estimation of PK Endpoints for Bioavailability

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
	100%	0.8743, 1.1438	0.2695
	110%	0.9617, 1.2582	0.2964
	120%	1.0492, 1.3725	0.3234
	130%	1.1366, 1.4869	0.3503
	150%	1.3114, 1.7157	0.4042

For the potential effect of PPI, a sample size of 9 PK evaluable participants will provide 90% CIs for the difference between treatments of ±0.2017 and ±0.2234 on the natural log scale for AUC_{inf} and C_{max}, respectively, with 80% coverage probability. Table 9 presents the width of 90% CI for different estimated effects.

Table 9. Confidence Interval Estimation of PK Endpoints for PPI Effect

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
AUC_{inf}	50%	0.4087, 0.6118	0.2031
	70%	0.5721, 0.8565	0.2844
	80%	0.6538, 0.9788	0.3250
	90%	0.7356, 1.1012	0.3656
	100%	0.8173, 1.2235	0.4062
	110%	0.8990, 1.3459	0.4469
	120%	0.9808, 1.4682	0.4875
	130%	1.0625, 1.5906	0.5281
	150%	1.2260, 1.8353	0.6093
C_{max}	50%	0.3999, 0.6251	0.2252
	70%	0.5599, 0.8752	0.3153
	80%	0.6399, 1.0002	0.3604
	90%	0.7198, 1.1252	0.4054
	100%	0.7998, 1.2503	0.4504
	110%	0.8798, 1.3753	0.4955
	120%	0.9598, 1.5003	0.5405
	130%	1.0398, 1.6254	0.5856
	150%	1.1997, 1.8754	0.6757

These calculations are based on estimates of within-participant standard deviation of 0.196 and 0.217 encorafenib for $\log_e AUC_{inf}$ and $\log_e C_{max}$ respectively, based on the results from crossover studies ARRAY-818-105 and ARRAY-162-105.

9.6. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that their personal study -related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant -specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant -specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.4. Committees Structure

10.1.4.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

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

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.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and IQMP maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant’s medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor's designee (Pfizer CRU).

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study -site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications, such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer-intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, and (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 10. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin <u>Laboratory:</u> Microscopy [a]	• COVID-19 PCR testing • Urine drug screening[c] • Urine cotinine • eGFR (calculated using CKD-EPI equation) <u>At screening only:</u> • FSH[b] • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency virus

a. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • 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 intervention.

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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 an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention 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 intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant'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 participant's condition. • Medical or surgical procedure (eg, 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.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 participant has been admitted (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 or significant 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 (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant 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.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention 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 intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant 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 or 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:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- 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.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their 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 intervention caused the event, then the event will be handled as "related to study intervention" 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.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the 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, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, 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.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception (refer to the list of highly effective methods below in Section 10.4.4), as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she:

is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not pregnant or breastfeeding

- Is not a WOCBP (see definitions below in Section 10.4.3).

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or female partners of male participants should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral + barrier*

    - Intravaginal + barrier*

    - Transdermal + barrier*

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral + barrier*

    - Injectable + barrier*

8. Sexual Abstinence

    Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated

in relation to the duration of the study and the preferred and usual lifestyle of the participant.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to encorafenib or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

- Retained samples will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: 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 participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 participant's individual baseline values and underlying conditions. Participants 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:

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

- For participants with baseline AST **OR** ALT **OR** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 participant 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 T bili for suspected Hy's law cases, 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, or 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, liver imaging (eg, 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 T bili 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.

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to estimate glomerular filtration rate [Scr-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline serum Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations[10]

2021 CKD-EPI Scr Only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ⩽ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽ 0.7	if ⩽ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ⩽ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ⩽ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ⩽ 0.9	if ⩽ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ⩽ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ⩽ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms 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 May Qualify as SAEs

• QTcF prolongation >500 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom -free participants 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 participants 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 (HR <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.

10.9. Appendix 9: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abs	absolute
ADL	activity/activities of daily living
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from 0 to time of last measurable concentration
AV	atrioventricular
BA	bioavailability
BE	bioequivalence
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
BRAF	B-RAF proto-oncogene, serine/threonine kinase
$BRAF^{mt}$	BRAF-mutated
CAP	encorafenib formulated capsule
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease - epidemiology
CL/F	apparent clearance of drug from eg, plasma
C_{max}	maximum observed concentration
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)
COT	cancer osaka thyroid
COVID-19	coronavirus disease 2019
CRAF	COT and RAF-1
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial

Abbreviation	Term
CTIS	Clinical Trial Information System
CTMS	Clinical Trial Management System
CV	cardiovascular
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DMID	dosage material identification
DU	dispensable unit
EC	ethics committee
EC50	half-maximal response concentration
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
CCI [redacted]	[redacted]
[redacted]	[redacted]
ERK	extracellular signal-regulated kinase
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F/U	follow-up
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
HBcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen

Abbreviation	Term
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HME	hot-melt extrudate
HR	heart rate
HRT	hormone replacement therapy
Ht	height
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IR	immediate release
IRB	Institutional Review Board
IRC	internal review committee
IV	intravenous(ly)
K	Proportionality constant for Bedside and Modified Schwartz Equations (kidney function)
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
K_3EDTA	tripotassium ethylenediaminetetraacetic acid
k_{el}	first-order elimination rate constant
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
LLNA	local lymph node assay
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
mCRC	metastatic colorectal cancer
MCV	mean corpuscular volume
MEK	mitogen-activated protein kinase
MQI	medically qualified individual
MTD	maximum tolerated dose
N/A	not applicable
Nab	neutralizing antibodies
NRU	neutral red uptake
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
PCR	polymerase chain reaction

Abbreviation	Term
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
pERK	phosphorylated ERK
pMEK	phosphorylated MEK
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PPI	proton-pump inhibitor
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
qual	qualitative
RAF	rapidly accelerated fibrosarcoma
rBA	relative bioavailability
RBC	red blood cell
RNA	ribonucleic acid
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SCL	supply chain lead
Scr	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal phase half-life
T^3	total triiodothyronine
TB	tuberculosis
T bili	total bilirubin
THC	tetrahydrocannabinol
T_{last}	time of the last quantifiable concentration [time]
T_{max}	time to reach C_{max}
TOC	table of contents
UGT	uridine 5'-diphospho-glucuronosyltransferase-glucuronosyltransferase
ULN	upper limit of normal

Abbreviation	Term
US	United States
USADE	unanticipated serious adverse device effect
USPI	United States Prescribing Information
UTI	urinary tract infection
V_z/F	apparent volume of distribution for extravascular dosing
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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