Clinical Trial Protocol C4221003 (ARRAY-818-103)

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

SAP – Statistical Analysis Plan Version 5.0

Approval Signatures

PPD

Date

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List of Abbreviations

ADaM	Analysis Data Model
AE	adverse event
Ae_{0-8}	amount eliminated via urine over an 8-hour period
ANOVA	analysis of variance
$AR_{AUClast}$	accumulation ratio of AUC_{last} on Day 14 compared to Day 1
AR_{Cmax}	accumulation ratio of C_{max} on Day 14 compared to Day 1
AUC	area under the curve
AUC_{last}	concentration time curve from time zero to the time of last quantifiable concentration
AUC_{inf}	concentration time curve from time zero extrapolated to infinity
$AUC_{\%extrap}$	percent of concentration time curve extrapolated
AUC_{tau}	AUC over the final dosing interval (tau)
BCRP	breast cancer resistance protein, sometimes referred to as ABCG2
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BRAF	BRAF proto-oncogene serine-threonine protein kinase
CI	confidence interval
CL/F	apparent total body clearance after extravascular administration
C_{max}	plasma maximum concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
$[CumA]_e$	cumulative amount excreted in urine during each collection interval
C_{urine}	urine concentration
CV	coefficient of variation
CYP	cytochrome P450 enzyme (1A2, 2B6, 2C9, 2C19, 2D6, 3A4, 3A5 refer to isoforms)
DDI	drug-drug interaction
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
[Fe]%	percentage of dose recovered in urine for a given drug or metabolite
FU	follow-up
GGT	gamma-glutamyl transferase
IR	immediate release
Kel	apparent terminal elimination rate constant
LH	luteinizing hormone
LHY746	encorafenib's metabolite
LLOQ	lower limit of quantitation
LSM	least squares means
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR	metabolite ratio

MR_{Ae0-8}	ratio of Ae_{0-8} values of the metabolite compared to parent
$MR_{AUClast}$	ratio of AUC_{last} values of the metabolite compared to parent
MR_{AUCinf}	ratio of AUC_{inf} values of the metabolite compared to parent
MR_{Cmax}	ratio of C_{max} values of the metabolite compared to parent
MUGA	multigated acquisition scan
NCI	National Cancer Institute
OATP	organic anion-transporting polypeptide
CCI	[redacted]
PK	pharmacokinetic(s)
PR	partial response
QD	once daily
QTcF	QT interval corrected for heart rate using the Fridericia formula
RBC	red blood cell(s)
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
$T_{1/2}$	terminal elimination half-life
TLF	tables, listings, and figures
T_{max}	time to the plasma maximum concentration
UDP	uridine diphosphate
UGT1A1	uridine diphosphate (UDP)-glucuronosyl transferase 1A1
Vol	collected urine volume during 0-8 hours post dose collection interval on Days -7, 1 and 14
V_Z/F	apparent total volume of distribution after extravascular administration
WBC	white blood cell(s)
WHO	World Health Organization

1 Introduction

This document provides the detailed statistical methodology for the analysis of data from study ARRAY-818-103. The table, listing, and figure shells of the statistical analysis plan (SAP) can be found in a separate SAP shell document.

The analyses described herein are based on protocol Version 8.0, dated 7DEC2020. All changes to the planned analysis described in this document will be made prior to database lock.

2 Study Objectives and Design

2.1 Study Objectives and Endpoints

The study objectives and corresponding endpoints are shown in the table below.

Table 2-1 Objectives and Related Endpoints

Objective	Endpoint
Primary	
• To evaluate the effect of single and multiple oral doses of encorafenib in combination with binimetinib on the single oral dose pharmacokinetics (PK) of the cytochrome P450 (CYP) enzyme probe substrates, losartan (CYP2C9), midazolam (CYP3A4), caffeine (CYP1A2), omeprazole (CYP2C19), and dextromethorphan (CYP2D6) and selected metabolites, in patients with BRAF V600-mutant unresectable or metastatic melanoma or other advanced solid tumors. • To evaluate the effect of single and multiple oral doses of encorafenib in combination with binimetinib on the single oral dose PK of rosuvastatin, an organic anion-transporting polypeptide (OATP) /breast cancer resistance protein (BCRP) substrate, and on the single oral dose PK of bupropion (a CYP2B6 substrate) and hydroxybupropion, in patients with	• Changes in plasma maximum concentration (C_{max}) and area under the concentration time curve from time zero to the time of last quantifiable concentration (AUC_{last}): midazolam, 1-hydroxymidazolam, caffeine, paraxanthine, omeprazole, 5-hydroxyomeprazole, rosuvastatin, bupropion and hydroxybupropion. • Changes in the amount eliminated via urine over an 8-hour period (Ae_{0-8}): losartan and its metabolite (E-3174), dextromethorphan and dextrorphan. • Changes in plasma encorafenib and LHY746 C_{max} and area under the concentration time curve (AUC) in Arm 3.

BRAF V600-mutant unresectable or metastatic melanoma or other advanced solid tumors. • To evaluate the effect of multiple doses of modafinil, a moderate CYP3A4 inducer, on the multiple oral dose PK of encorafenib and its metabolite, LHY746, in patients with BRAF V600-mutant unresectable or metastatic melanoma or other advanced solid tumors.	

Secondary	
• To assess the single and multiple dose PK of encorafenib, LHY746 and binimetinib (and its metabolite, AR00426032) after coadministration with a single oral dose of the CYP probe cocktail, rosuvastatin, and bupropion.	• Metabolite ratios (MR_{AUC} and MR_{Cmax}) for 1-hydroxymidazolam/midazolam, paraxanthine/caffeine, 5-hydroxy omeprazole/omeprazole, hydroxybupropion/bupropion and LHY746/encorafenib and MR_{Ae0-8} for E-3174/losartan and dextrorphan/dextromethorphan. • Pharmacokinetic parameters (e.g., time to reach C_{max} [T_{max}], AUC from time zero extrapolated to infinity [AUC_{inf}], percent of AUC extrapolated [$AUC_{\%extrap}$], apparent terminal elimination rate constant [Kel], apparent terminal elimination half-life [$T_{1/2}$], apparent total body clearance after extravascular administration [CL/F], and apparent total volume of distribution after extravascular administration [V_z/F]) where calculable, for midazolam, 1-hydroxymidazolam, caffeine, paraxanthine, omeprazole, 5-hydroxy omeprazole, rosuvastatin, bupropion and hydroxybupropion. • Pharmacokinetic parameters (e.g., urine concentration [C_{urine}], quantity of urine excreted during each collection interval [Vol], cumulative amount excreted in urine during each collection interval $[CumA]_e$, and percentage of dose recovered in urine [Fe] %) for losartan, E-3174, dextromethorphan and dextrorphan. Pharmacokinetic parameters (e.g., C_{max}, AUC_{last}, T_{max}, AUC_{inf}, $AUC_{\%extrap}$, Kel, $T_{1/2}$, CL/F, and V_z/F) for encorafenib, LHY746, binimetinib and AR00426032 where calculable.

• To assess the safety and tolerability of single and multiple oral doses of encorafenib in combination with binimetinib when administered with a single oral dose of the CYP probe cocktail, rosuvastatin and bupropion during the drug-drug interaction (DDI) portion of the study. • To assess safety and tolerability of multiple oral doses of encorafenib in combination with binimetinib when administered with multiple doses of modafinil during the DDI portion of the study.	• Safety will be evaluated by monitoring adverse events (AEs), physical examinations, ophthalmic examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), echocardiogram (ECHO)/multigated acquisition scan (MUGA), and clinical laboratory tests.
CCI [redacted]	
• [redacted]	• [redacted]

2.2 Study Design

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

The study will have 2 treatment phases, a drug-drug interaction (DDI) phase followed by a post-DDI phase. The DDI phase is from Day -7 to Day 28 Visit for Arm 1 and Arm 2, and from Day 1 to Day 28 Visit for Arm 3. The DDI visit days are -7, 1, 14 and 28 for Arm 1 and Arm 2, and Days 1, 14, 15, 21 and 28 for Arm 3, respectively. During the DDI phase patients will receive the CYP probe drug cocktail (Arm 1), the OATP/BCRP probe substrate, rosuvastatin and CYP2B6 substrate, bupropion (Arm 2), or the CYP3A4 inducer, modafinil (Arm 3) and encorafenib in combination with binimetinib.

During the post-DDI phase patients may continue to receive treatment with encorafenib in combination with binimetinib until treatment discontinuation criteria are met. The combination of encorafenib 450 mg once daily (QD) and binimetinib 45 mg twice daily (BID) has been

evaluated in over 300 patients with BRAF V600 mutant melanoma in previous studies including 192 patients in the pivotal Phase 3 trial, COLUMBUS. Since the safety and efficacy of the combination has already been extensively studied in previous trials, in the post-DDI phase of the current trial, patients will be treated as per local standard-of-care practice for patients with BRAF V600-mutant unresectable or metastatic melanoma or other advanced solid tumors and only limited data will be collected. The data collection required in the post-DDI phase will include concomitant medications and administration of encorafenib and binimetinib as well as tumor assessments. There will also be collection of all AEs and all serious adverse events (SAEs). Other safety evaluations conducted are not required to be reported in the CRF.

2.2.1 DDI Phase

The study schema for Arm 1, Arm 2 and Arm 3 are presented in Figure 2-1.

For each individual patient, the DDI phase starts on the day of the first study drug dose and ends on the day of the Day 28 Visit conducted before Day 35. In the scenario that Day 28 assessments are not all completed on the same day, the date of the latest assessment required for the Day 28 Visit performed before Day 35 will be considered as the end of DDI phase for that patient.

Arm 1

Patients will receive a single oral dose of the CYP probe cocktail (losartan, midazolam, caffeine, omeprazole, and dextromethorphan) on Day -7. Encorafenib, administered 450 mg QD and binimetinib, administered 45 mg BID will be initiated on Day 1. Patients will then receive a single oral dose of the CYP probe cocktail on Day 1 and Day 14 within 5 minutes after the encorafenib/binimetinib administration. Blood and urine PK sampling will be conducted from 0 to 8 hours on Day -7, Day 1 and Day 14. Arm 1 will enroll 20 subjects.

Arm 2

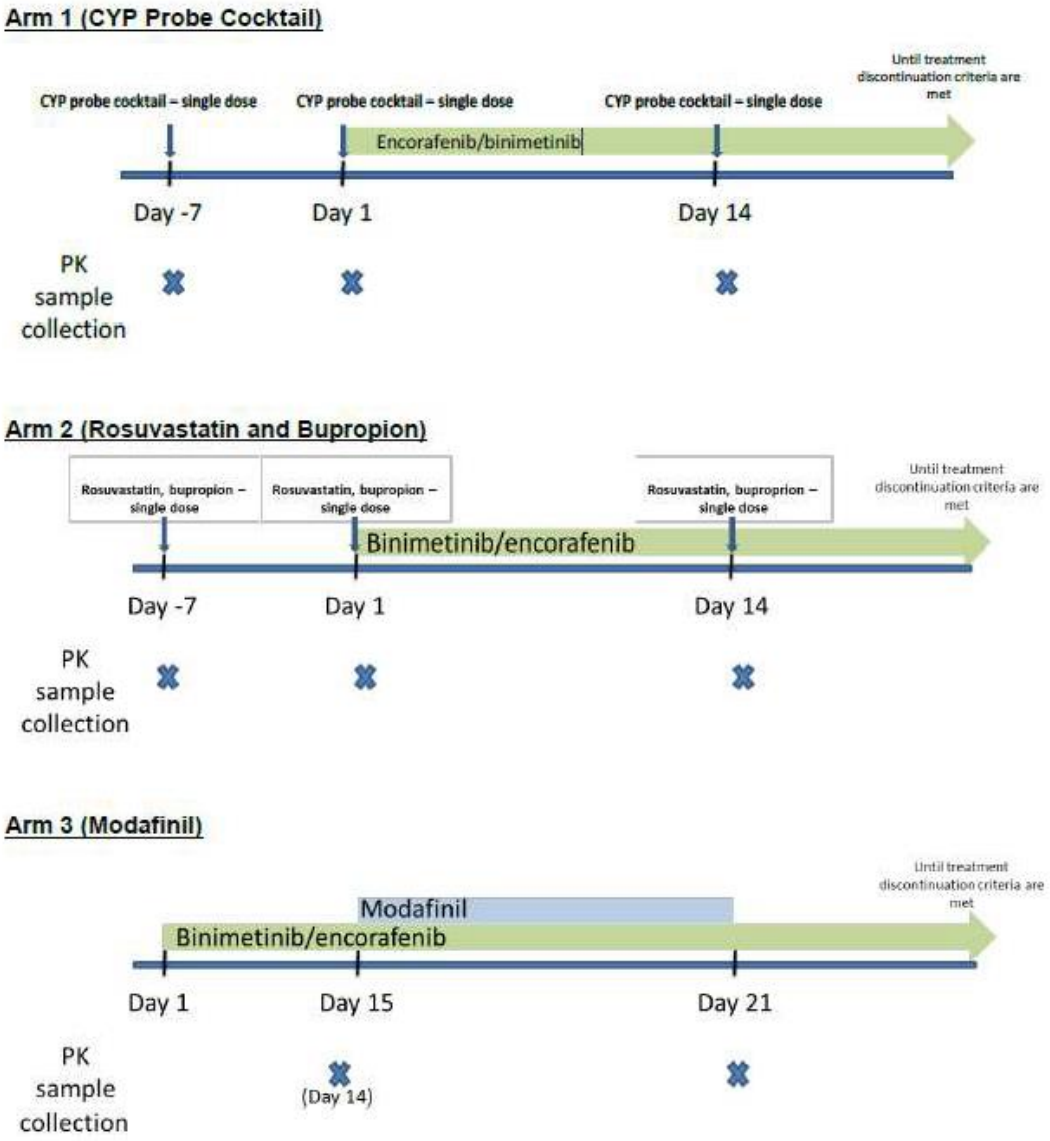
Patients will receive a single oral dose of rosuvastatin and bupropion Day -7. Encorafenib, administered 450 mg QD and binimetinib, administered 45 mg BID will be initiated on Day 1. Patients will then receive a single oral dose of rosuvastatin and bupropion on Day 1 and Day 14 within 5 minutes after the encorafenib/binimetinib administration. Blood PK sampling will be conducted from 0 to 8 hours on Day -7, Day 1, and Day 14. Arm 2 will enroll 10 subjects.

Arm 3

Patients will start continuous treatment with encorafenib 450 mg QD and binimetinib 45 mg BID on Day 1. Patients will then receive continuous treatment of modafinil on Day 15 through Day 21. Blood PK sampling will be conducted from 0 to 8 hours on Day 14 and Day 21. Arm 3 will enroll 6 to 12 subjects.

On each arm, all drugs will be taken within 10 minutes total time.

Figure 2-1 Study Schema



2.2.2 Post-DDI Phase

During the post-DDI phase, patients may continue to receive the encorafenib/binimetinib combination as long as none of the treatment discontinuation criteria are met: disease progression, AE requiring discontinuation of study drugs or rendering the patient unsuitable for further treatment, withdrawal of consent, pregnancy, significant protocol deviation(s), loss to follow up, Investigator decision, death, or study termination by Sponsor. If patients choose to not continue in the post-DDI phase, the Day 30 Safety Follow-up Visit assessments will be performed.

If a patient in the post-DDI phase permanently discontinues treatment with binimetinib, he/she may continue treatment with encorafenib as monotherapy at its recommended Phase 2 dose (RP2D) of 300 mg QD. However, due to the limited efficacy of binimetinib alone in previous study populations, if a patient permanently discontinues treatment with encorafenib, he/she must discontinue treatment with binimetinib and complete the Day 30 Safety Follow-up Visit.

It is recommended that patients be evaluated according to standard practice during the post-DDI phase. Safety should be monitored by assessing physical examinations, hematology and chemistry laboratory results and any other pertinent results required as part of the safety profile of the compound (e.g., dermatological examinations, ophthalmic exams, cardiac profiles) until discontinuation. Adverse events will be collected at every visit. In the post-DDI phase, all AEs and all SAEs will be captured on the AE CRF and SAEs will be reported to the Sponsor or designee using the SAE form.

The recommended timelines for the reviews and examinations are as follows:

- Every 3-4 weeks:
  - Review of concomitant medications
  - Review of AEs
  - Physical examination, hematology and chemistry laboratory testing
  - If clinically indicated: triplicate 12-lead electrocardiogram (ECG) within approximately 5 to 10 minutes total time
  - Assess compliance with administration of encorafenib and binimetinib
- Every 8-12 weeks:
  - Efficacy assessment in order to assess continued benefit
  - Echocardiogram (ECHO)/multigated acquisition scan (MUGA) (more frequent if clinically indicated)
  - Ophthalmic examination (and as clinically indicated if visual symptoms are reported)
  - Dermatologic examination every 8 weeks to be continued up to 6 months after discontinuing encorafenib

2.3 Sample Size Justification

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

For Arm 2 (rosuvastatin and bupropion), the CV of the ratio between 2 rosuvastatin AUC_{last} values for the same patient is approximately 47% (Stopfer 2016). Assuming a 2-sided significance level of 0.05 and a power of 0.8, approximately 10 patients would need to be evaluable to detect a difference of 50% in mean AUC_{last}. Assuming an intrapatient variation of

23% for bupropion AUC_{0-8} (Bosilkovska 2014), there is an 80% probability with 10 patients that a treatment difference will be detected if the true effect size is 33%.

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

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

2.4 Analysis Sets

2.4.1 All Enrolled Set

For Arm 1 only, all patients who receive at least one dose of any study drug will be included in the All Enrolled Set.

2.4.2 Safety Set

For all arms, all patients who receive at least one dose of encorafenib and/or binimetinib will be included in the Safety Set.

2.4.3 Pharmacokinetic Set

The Pharmacokinetic (PK) Set includes all patients who receive at least one dose of any study drug and have at least one post-baseline PK sample with an associated bioanalytical result. The PK Set will be used for summaries of concentration data, summaries of PK parameters, plots of individual concentration data and PK parameters and all PK listings. Additional exclusions may be applied to the PK Set on a per analyte basis at the discretion of the Pharmacokineticist.

2.4.4 Evaluable Pharmacokinetic Set

The Evaluable PK Set includes all patients in the PK Set with sufficient concentration data to calculate at least one PK parameter for a probe drug on Days -7, 1, and 14 (for binimetinib and encorafenib on Days 1 and 14 [Arm 1 and Arm 2] and for binimetinib and encorafenib on Days 14 and 21 [Arm 3]). Patients who discontinue or require a dose reduction of encorafenib prior to completion of the last PK sampling on Day 14 in Arms 1 and 2 or on Day 21 in Arm 3 may be considered unevaluable for PK analyses and may be replaced at the discretion of the Pharmacokineticist. If a patient misses 3 or more consecutive doses of encorafenib in any arm or 3 or more consecutive doses of modafinil in Arm 3 prior to completion of the last PK sampling on Day 14 in Arms 1 and 2 or on Day 21 in Arm 3, the patient may be excluded from Evaluable PK set at the discretion of the Pharmacokineticist. In addition, patients who miss any dose of study drugs on any of the PK days, or who vomit within 4 hours after dosing on any of the PK days may be replaced but may be excluded from Evaluable PK set at the discretion of the Pharmacokineticist. Patients who are excluded due to the above reasons will be excluded from the Evaluable PK Set which will be used for summaries of concentration

data and plots of summarized concentration data, and summaries of PK parameters, statistical analyses, and plots of summarized PK parameters. Additional exclusions may be applied to the Evaluable PK Set on a per analyte basis at the discretion of the Pharmacokineticist. Full details will be recorded in the CSR.

2.5 Treatment Assignment

2.5.1 Doses and Schedule of Administration

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

- 25 mg losartan oral tablet (50 mg losartan prior to protocol Version 5)
- 30 mg dextromethorphan oral capsule
- 50 mg caffeine as oral liquid (100 mg caffeine, 20 mg/mL oral liquid prior to protocol Version 5)
- 20 mg omeprazole oral capsule
- 2 mg midazolam oral syrup

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

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

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

- 400 mg (2 × 200 mg) modafinil tablets QD

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

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

2.5.2 Duration of Treatment

For encorafenib/binimetinib:

- Duration of exposure (days) = date of last (non-zero) dose of study drug – date of first dose of study drug + 1.

See Section 2.7.5 for imputation rules of last date of study drug administration.

2.5.3 Cumulative Dose

For encorafenib/binimetinib:

- Cumulative dose (mg) = sum of all actual doses taken during the dosing period.

2.5.4 Dose Intensity and Relative Dose Intensity

For encorafenib/binimetinib:

- Planned dose intensity (mg/day) = is 450 mg/day (450 mg QD) for encorafenib and 90 mg/day (45 mg BID) for binimetinib;
- Dose intensity (mg/day) = cumulative dose (mg) / duration of exposure (days);
- Relative dose intensity = 100*[Dose intensity (mg/day) / planned dose intensity (mg/day)].

A summary of exposure, including duration, dose intensity, and relative dose intensity (including categories <50%, 50%-<75%, 75%-<90%, 90%-<110% and ≥110%, if applicable), will be presented for encorafenib and binimetinib by treatment arm and overall. Date and time of administration of CYP probe cocktail, rosuvastatin, bupropion, modafinil, binimetinib, and encorafenib will be listed. Duration of exposure, cumulative dose, dose intensity, and relative dose intensity will be listed for binimetinib and encorafenib for each patient by treatment group.

2.5.5 Dose Modifications

For patients who do not tolerate the encorafenib and/or binimetinib initial dosing schedule, dose reduction is permitted to allow the patient to continue on study drug. Patients who require a dose reduction of study drug(s), in particular encorafenib, prior to completion of the last PK sampling on Day 14 in Arms 1 and 2 or on Day 21 in Arm 3 may be considered to be unevaluable for PK analyses and may be replaced at the discretion of PK analyst. A detailed dose modification and reduction plan is presented in Section 6.5 of the protocol. Dose modifications will be summarized in tables and dose modification details will be provided in the listings.

Dose Reduction:
A dose reduction is defined as a decrease in dose from the protocol planned dose (450 mg QD encorafenib or 45 mg BID binimetinib) or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. For example, for encorafenib, in the sequence of total daily dose 450 mg – 0 mg – 300 mg, the 300 mg dose will be counted as a reduction.

If a patient moves from a higher than protocol planned dose down to the planned dose then this is not to be counted as a reduction, however if the patient moves directly from a higher than planned dose down to a lower than protocol planned dose, then this is counted as a reduction.

If the dose on the first dosing record is lower than protocol planned dose this is also counted as a reduction.

Dose Interruption:

For encorafenib/binimetinib, a dose interruption is defined as an actual dose equal to zero(where the planned dose is not zero), between the first and the last non-zero doses, following a non-zero actual dose.

Frequency counts and percentages of patients who have encorafenib/binimetinib dose reductions or interruptions, and the corresponding reasons, will be provided separately. The number of dose interruptions per patient, and the duration of dose interruptions (days) will also

be summarized. Dose administration details for CYP probe cocktail, rosuvastatin/buproprion, modafinil, and encorafenib/binimetinib will be provided in listings.

2.6 Center Pooling Method

The data from participating centers will be combined, so that an adequate number of patients will be available for analysis. Due to the small number of patients expected per center, no center effect will be assessed.

2.7 Imputation Rules for Partial or Missing Dates

For computation of time intervals (e.g., elapsed time between initial diagnosis and first recurrence/relapse), the time interval should be set to missing when the imputation rule leads to a negative value.

For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event.

For AEs, concomitant medications, and antineoplastic therapies, imputation rules for partial or missing dates are described below.

For imputations that are based on last contact date, note that last contact date will be derived for patients not known to have died on or before the analysis cutoff date. Imputed dates will not be considered for the determination of last contact date. Only dates associated with patient visits or actual assessment of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status (e.g., the date a blood sample was processed) will not be used. Assessment dates after the cutoff date will not be applied to derive the last contact date. Last contact date will only be derived using the latest complete date among the following:

- Study drug start and end dates with non-missing dose (doses of 0 are allowed)
- RECIST assessment date with evaluation marked as done
- Laboratory/PK collection date with sample collection marked as done
- Vital sign, ECG, physical exam and ophthalmic exam assessment date with non-missing parameter value
- Performance status date with non-missing performance status
- Start/end date of AEs with non-missing verbatim term
- Start/end date of antineoplastic therapies administered after study treatment; discontinuation with non-missing medication/procedure term
- Cardiac imaging assessment date
- CCI [redacted]

2.7.1 Concomitant Medication Date Imputation

Incomplete concomitant medication dates will be imputed as follows:

Medication start date

- If only day is missing,

  - If month and year match that of the treatment start date, impute as (treatment start date + 1).
  - If month and year is prior to the treatment start date, impute as the 15th day of the month.
  - If month and year is after the treatment start date, impute as the first day of the month.
- If both day and month are missing,
  - If the year matches that of the treatment start date, impute as (treatment start date + 1).
  - If the year is prior to the treatment start date, impute as July 1
  - If the year is after the treatment start date, impute as January 1
- In all other cases the incomplete medication start date will not be imputed.

Medication end date

- If only day is missing,
  - If month and year match that of last contact date, and the medication is ongoing, impute as the last day of the month. Otherwise, impute as last contact date.
  - If month and year is prior to last contact date, impute as the last day of the month.
- If both day and month are missing,
  - If the year matches that of last contact date, and the medication is ongoing, impute as December 31. Otherwise, impute as last contact date.
  - If the year is prior to or after last contact date, impute as December 31.
- If the medication end date is completely missing and the medication is ongoing, impute as last contact date.
- In all other cases the incomplete medication end date will not be imputed.

Table 2-2 and Table 2-3 provide examples for different scenarios of imputing concomitant medication start and end dates, respectively.

Table 2-2 Concomitant Medication Start Date Imputation Example Scenarios

Partial Concomitant Medication Start Date	Treatment Start Date	Temporal Relationship Compared to Treatment Start	Imputed Date
12mmyyyy	20OCT2001	Uncertain	<blank>

Partial Concomitant Medication Start Date	Treatment Start Date	Temporal Relationship Compared to Treatment Start	Imputed Date
ddmmm2000	20OCT2001	Before	01JUL2000
ddmmm2002	20OCT2001	After	01JAN2002
ddmmm2001	20OCT2001	Uncertain	21OCT2001
ddSEP2001	20OCT2001	Before	15SEP2001
ddOCT2001	20OCT2001	Uncertain	21OCT2001
ddNOV2001	20OCT2001	After	01NOV2001

Table 2-3 Concomitant Medication End Date Imputation Example Scenarios

Partial Concomitant Medication End Date	Minimum (Last Contact date, 30-Day FU Date)	Ongoing	Imputed Date
Missing	20OCT2001	Yes	20OCT2001
ddmmm2000	20OCT2001	No	31DEC2000
ddmmm2002	20OCT2001	No	31DEC2002
ddmmm2001	20OCT2001	No	20OCT2001
ddmmm2001	20OCT2001	Yes	31DEC2001
ddSEP2001	20OCT2001	No	30SEP2001
ddOCT2001	20OCT2001	No	20OCT2001
ddOCT2001	20OCT2001	Yes	31OCT2001

2.7.2 Adverse Event Date Imputation

The imputation of the start date and end date of AEs will follow the same conventions as for the concomitant medication start and end dates. AEs that are completely missing a start date will be considered as treatment emergent if the end date of the AE is either missing or occurs after the treatment start date. In this case, the AE start date will be imputed to be the treatment start date.

2.7.3 Antineoplastic Therapies Date Imputation

Prior Therapies

Start date:

In general, the same rules for imputation of an AE and concomitant medication start date will be followed, except:

- Completely missing start dates:

- Impute as treatment start date - 1.

- Partial missing start dates:
  - If only day is missing and month and year match that of the treatment start date, impute as treatment start date - 1;
  - If day and month are missing, and the year matches that of the treatment start date, impute as treatment start date - 1.

End date:

- Completely missing end dates:
  - Do not impute
- Partial missing end dates:
  - Imputed date = min(treatment start date - 1, last day of the month), if day is missing;
  - Imputed date = min(treatment start date - 1, 31DEC), if month and day are missing.

Post Therapies

Start date:

- Completely missing start dates:
  - Impute as last date of study drug + 1.
- Partial missing start dates:
  - Imputed date = max(last date of study drug + 1, first day of the month), if day is missing;
  - Imputed date = max(last date of study drug + 1, 01JAN), if day and month are missing.

Last date of study drug is the date of treatment discontinuation as collected from the disposition page.

End date:

No imputation.

2.7.4 Date of Initial Diagnosis of Cancer, and Date of Most Recent Recurrence

Initial Diagnosis of Cancer

- Incomplete dates will be imputed as follows:
  - If only day is missing, impute as 15.
  - If both day and month are missing, and the year is prior to the year of first dose start date, impute as July 1.
  - If both day and month are missing and the year is same as the year of the first dose date, imputed as January 1.

- If the date is completely missing, no imputation will be performed.

Date of Most Recent Recurrence

- Incomplete dates will be imputed as follows:
  - If only day is missing, impute as 15.
  - If both day and month are missing, and year matches that of the first study treatment, impute as max (initial diagnosis date, January 1).
  - If both day and month are missing, and year is prior to the year of first study treatment, impute as max (initial diagnosis date, July 1).
  - If the date is completely missing, no imputation will be performed.

2.7.5 Imputation of Last Date of Study Drug Administration

If the last date of study drug is completely missing and there is no end of treatment electronic case report form (eCRF) page and no death date, the patient should be considered as on-going and use the cut-off date for the analysis as the last dosing date.

If the last date of study drug is completely or partially missing and there is either an end of treatment eCRF page or a death date, then imputed last dose date will be as follows:

- = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)
- = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)
- = Last day of the month, if both Year and Month are available and Year < Year of min (EOT date, death date)
- = min (EOT date, death date), for all other cases

The imputed date will be compared with start date of study treatment:

- If the imputed date < start date of study drug, then last date of study drug is set to start date of study drug;
- Otherwise, use the imputed date.

2.7.6 Incomplete Death Date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is completely missing, it will be imputed as the day after last contact date.
  - Note: A special case is the patient's last contact date is the same as the data cutoff date. In this case, the patient's death date will be imputed as the day after the last contact date. Therefore, he would be still alive as of the data cutoff date.

- If the day or both day and month are missing, death date will be imputed to the maximum of the full (non-imputed) [last contact date (excluding the date of death) + 1] and the following:
  - Missing day: 15th day of the month and year of death
  - Missing day and month: July 1 of the year of death

2.7.7 Incomplete Assessment Dates

No incomplete assessment dates will be imputed.

2.8 Imputation Rules for Other Missing Data

Other missing data will simply be noted as missing on appropriate tables/listings.

2.9 Subgroup Analyses

The study data for Arm 2 will be summarized by Non-Asian and Overall subgroups.

3 Data Analysis Methods

The study data will be analyzed and reported based on all patients' data. Categorical data will be presented as frequencies and percentages. For continuous data, mean, SD, median, minimum, and maximum will be presented.

3.1 Definitions

3.1.1 Study Day

Study day is defined in the following manner:

- Study Day 1 is defined as start date for encorafenib/binimetinib. In Arm 1, if encorafenib/binimetinib was not administered, Study Day 1 will be defined as the date the CYP probe cocktail was administered.
- On or after Study Day 1: the study day will be calculated as (date of assessment) – (date of Study Day 1) + 1.
- Before Study Day 1: the study day will be calculated as (date of assessment) – (date of Study Day 1).

3.1.2 Observation Period

The overall observation period includes the DDI phase and post-DDI phase as defined in Section 2.2. AEs in DDI phase and post-DDI phase will be summarized separately. For other safety summary tables, any safety assessments beginning from Day -7 for Arm 1 and Arm 2, and from Day 1 for Arm 3, respectively, to the end of DDI phase will be considered.

All data, regardless of observation period, will be listed.

3.1.3 Baseline

Baseline is the last available and valid assessment performed before the first administration of any study treatment, unless otherwise stated under the related assessment section of the protocol

and/or the SAP. Baseline can be the day before first treatment administration or the same day as first treatment administration if a predose assessment/value is available (e.g., ECG, PK samples, CCI).

If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment will be considered as baseline only if it is actually performed before the first dose, as checked using both times (i.e., time of the first treatment dose and time of the assessment).

If no time is provided for an assessment on the day of the first administration of the study treatment, it will be treated as predose assessment.

Patients with no data on a particular parameter before the first treatment administration will have a missing baseline for this parameter.

For safety comparisons with baseline (e.g., for laboratory parameters, vital signs, weight, etc.), baseline is considered as the last available assessment or value collected prior to start of treatment. If no time is provided for an assessment on the day of the first administration of the study treatment, it will be treated as predose assessment.

The ECG baseline will be the average of triplicate ECG measurements prior to the start of treatment.

3.2 Patient Demographics and Other Baseline Characteristics

Unless specified otherwise, summary tables described in this section will be based on the Safety set and listings will be based on All Enrolled set for Arm 1 to include those participants who were enrolled but did not receive encorafenib and/or binimetinib and Safety set for Arms 2 and 3.

3.2.1 Demographics and Baseline Characteristics

Demographic, and other baseline data including age, gender, race, ethnicity, height, weight, body mass index (BMI) = weight (kg)/height^2 (m^2), and Eastern Cooperative Oncology Group (ECOG) performance status will be listed individually by patient and summarized by study arm using descriptive statistics (continuous data) or contingency tables (categorical data). Additionally, smoking status (non-smoker, occasional smoker, or smoker) will be individually listed by patient and summarized by study arm for Arms 2 and 3.

3.2.2 Patient Disposition

The number and percent of patients in safety analysis set will be summarized separately for DDI phase and post-DDI phase:

- Number (%) of patients who discontinued the study treatment;
- Number (%) of patients who are still on-treatment;
- Number (%) of patients who completed treatment;
- Primary reasons for treatment discontinuation;
- Number (%) of patients who completed the study;

- Primary reasons for study phase completion.

For Arm 1, below additional summary will be included based on All enrolled set.

- Number (%) of patients who discontinued the study treatment prior to encorafenib and/or binimetinib;
- Number (%) of patients who received at least one dose of encorafenib and/or binimetinib;
- Primary reasons for treatment discontinuation prior to encorafenib and/or binimetinib;
- Primary reasons for study discontinuation prior to encorafenib and/or binimetinib.

Patient disposition will also be listed.

3.2.3 Protocol Deviations

All protocol deviations will be finalized before database lock. Reasons for exclusions from populations will be listed by patient. All protocol deviations will be listed. In addition, a separate listing will be created for protocol deviations related to COVID-19.

3.2.4 Medical History

Past and current medical history will be summarized and listed. The summary will be presented by primary system organ class and preferred term. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) as per latest version available at time of database lock.

3.2.5 Disease History

Tumor types and their stages at the study entry will be summarized. The details of disease history including primary site of cancer, histological grade, predominant histology/cytology, additional histology/cytology, stage grouping at initial diagnosis, primary tumor stage initial diagnosis, lymph nodes stage at initial diagnosis, metastases stage at initial diagnosis, stage grouping at study entry, primary tumor stage at study entry, lymph nodes stage at study entry, metastases stage at study entry, metastases sites, time from initial diagnosis of primary site to start of study treatment (months), and time from most recent relapse/progression to start of study treatment (months) will be listed. Days will be converted to months by dividing the number of days by 30.4375.

Incomplete dates will be handled as described in Section 2.7.4.

3.2.6 Prior Antineoplastic Therapy

Prior anti-neoplastic therapies will be listed and the latest therapy will be summarized in three separate tables for medications, radiotherapy, and surgery.

- For medications, the total number of medication regimens along with its descriptive statistics, the setting (e.g., adjuvant), the best response, duration of best response, reason for discontinuation of therapy, and time between end of last medication to start of treatment

(using continuous statistics and categories: <1 month, 1- <6 months, 6- <12 months, ≥12 months) will be summarized by treatment arm.

- For radiotherapy, the location, setting (e.g., neoadjuvant), method, time between end of last radiotherapy to start of treatment (as categories: <1 month, 1- <6 months, 6- <12 months, ≥12 months) and prior radiotherapy 30% of bone marrow will be summarized by treatment arm.
- For surgery, procedure and the time since last surgery to start of treatment (as categories: <1 month, 1- <6 months, 6- <12 months, ≥12 months) will be summarized by treatment arm.

Incomplete dates will be handled as described in Section 2.7.3. Days will be converted to months by dividing the number of days by 30.4375.

3.2.7 Concomitant Therapy

Concomitant therapies are defined as any medications (excluding study drug and prior antineoplastic treatments), and significant non-drug therapies administered in the study. Concomitant therapies are recorded in the "Prior and Concomitant Medications" and the "Surgical and Medical Procedures" eCRF, respectively. Concomitant therapies will be coded using the latest version of the World Health Organization (WHO) Drug Dictionary available prior to database lock.

Concomitant therapies will be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred term. These summaries will include

1) Medications starting on or after the start of study treatment but starting no later than 30 days after last dose of study drug and
2) Medications starting prior to the start of study drug and continuing after the start of study treatment.

All concomitant medications will be listed. Those collected during the post-DDI phase are to be flagged. Incomplete dates will be handled as described in Section 2.7.1.

Prohibited concomitant medications are specified in the protocol. Several general and arm-specific exclusion criteria involve prohibited concomitant medications and are referred to in general and treatment arm-specific exclusion criteria. No separate outputs will be produced related specifically to prohibited concomitant medications.

3.3 Safety Analysis

The Safety Set will be used in all safety tables and listings for Arms 2 and 3. The All Enrolled set will be used in all safety listings for Arm 1.

In all three arms, all safety data will be recorded in the patient's source documents and eCRF. The assessment of safety will be based on AEs (including SAEs), laboratory profiles (hematology, biochemistry, coagulation, cardiac/muscle enzymes, and urinalysis), physical examination (including vital signs, ophthalmic and dermatological examinations), and cardiac profiles (ECG and MUGA or ECHO). A listing will be generated for study disruptions due to COVID-19 including protocol deviations, adverse events, treatment discontinuation, study

discontinuation and deaths. All safety data will be listed and summarized as detailed in the sections below.

3.3.1 Adverse Events

An AE is any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient administered a pharmaceutical product regardless of causality. Adverse events will be assessed by direct observation and patient interviews. Patients should be questioned using non-leading questions.

Adverse events will be coded using MedDRA as per latest version available at time of database lock. The severity of each AE will be categorized using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v4.03. The severity rating of an AE refers to its intensity.

Treatment-emergent AEs (TEAEs) will be defined as:

- Any new event that starts after the 1st administration of encorafenib/binimetinib and ≤30 days after treatment discontinuation
- Any event that was ongoing when treatment with study drug started and the severity/grade after treatment was higher than the Baseline value (fluctuations below the Baseline severity/grade are not considered as treatment emergent)
- Any new event that starts >30 days after treatment discontinuation and is assessed by the Investigator as related to study treatment.
- Any new event that is completely missing a start date and the end date is either missing or occurs after the treatment start date

Only Treatment-emergent AE summaries will be produced as follows:

- Overall summary of AEs, including the number and percentage of patients with at least one AE, SAE, AE leading to study drug discontinuation, AE leading to dose interruption/dose reduction, and AE leading to additional therapy. Summaries will be provided for all AEs and AEs suspected to be related to study drug. The number of on-treatment deaths will also be summarized
- AEs, regardless of study drug relationship by primary system organ class and preferred term (overall and Grade 3 or higher)
- AEs, regardless of study drug relationship by preferred term (overall and Grade 3 or higher)
- AEs with suspected study drug relationship by primary system organ class and preferred term (overall and Grade 3 or higher)
- AEs with suspected study drug relationship by preferred term (overall and Grade 3 or higher)
- AEs, regardless of study drug relationship by primary system organ class, preferred term and maximum grade
- SAEs, regardless of study drug relationship, by primary system organ class and preferred term (overall and Grade 3 or higher)

- SAEs with suspected study drug relationship, by primary system organ class and preferred term (overall and Grade 3 or higher)
- Non-SAEs, regardless of study drug relationship, by primary system organ class and preferred term (overall and Grade 3 or higher)
- AEs leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term (overall and Grade 3 or higher)
- AEs requiring dose reduction or study-drug interruption, regardless of study drug relationship, by primary system organ class and preferred term (overall and Grade 3 or higher)
- Deaths (on treatment), by primary system organ class and preferred term.

Treatment-emergent AEs, as defined above, in the DDI phase and the post-DDI phase will be summarized separately; treatment-emergent AEs in the DDI phase will be included in these summaries regardless of whether the patient participates in the post-DDI phase. For patients who do not enter post-DDI phase, AEs that occur within 30 days after the last DDI dose and AEs that occur at >30 days that are study drug related will be reported in DDI phase tables. Adverse Events will be counted only in the phase in which the AE began. For the post-DDI phase, only Grade 3 and 4 AEs and SAEs will be summarized. All AEs and SAEs will be listed and AEs collected during the post-DDI phase will be flagged. Listings of all deaths, SAEs, and AEs leading to study drug discontinuation will also be provided.

Incomplete dates will be handled as described in Section 2.7.2.

3.3.2 Physical Examinations

Physical examination dates will be presented in a data listing. Any clinically-relevant abnormal findings reported as AEs will be reported in the appropriate AE listings and summary tables.

3.3.3 Ophthalmic Examinations

All ophthalmic examinations (i.e., visual acuity, fundoscopy examination, slit lamp examination, optical coherence tomography, fluorescein angiography, and intraocular pressure assessment) will be listed.

3.3.4 Electrocardiograms (ECGs)

Triplicate 12-lead ECGs will be performed as specified in Table 7 (Arms 1 and 2) and Table 8 (Arm 3) in the protocol. Triplicate 12-lead ECGs will be performed at predose (up to 30 minutes before any study drug administration) and for all protocol-specified post-baseline assessments. Post-dose ECGs are to be performed at all protocol-specified, post-baseline assessments (± 30 minutes). Triplicate 12-lead ECGs are to be performed during the post-DDI phase if clinically indicated.

The mean of the triplicate ECG measurements performed at baseline and postdose will serve as each patient's baseline value and post-dose values for comparisons.

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

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

The following summaries will be provided for each applicable ECG parameter:

- Descriptive statistics at baseline, worst post-baseline and change from baseline to worst value in terms of absolute change. The highest post-baseline value for QT, QTcF, heart rate, PR, and QRS will be considered as the worst value.
- Frequency counts and percentages of patients having notable ECG values according to Table 3-1.

Table 3-1 Criteria for Notable ECG Values

ECG parameter	Criteria for ECG notable values
QT, QTcF (ms)	Increase from baseline >30-60 ms, >60 ms New QT interval >450-480, >480-500, >500 ms
HR (bpm)	Increase from baseline >25% and value >100 bpm Decrease from baseline >25% and value <60 bpm
PR (ms)	Increase from baseline >25% and value >200 ms
QRS (ms)	Increase from baseline >25% and value >110 ms

ECG evaluations will be listed and notable ECG values (including notable QT interval values) will be flagged in the listings.

3.3.5 MUGA/Echocardiogram

Left ventricular ejection fraction (LVEF) abnormalities will be defined according to CTCAE grade Version 4.03. Patients will be considered as having a LVEF abnormality if the worst post-baseline value is Grade 2, 3, or 4 according to the following classification:

- Grade 0: Non-missing value below Grade 2;
- Grade 2: LVEF between 40% and 50% or absolute change from baseline between -10% and <-20%;
- Grade 3: LVEF between 20% and 39% or absolute change from baseline lower than or equal to -20%;
- Grade 4: LVEF lower than 20%.

The following summaries will be produced for LVEF by treatment arm:

- Descriptive statistics at baseline, at Day 28 Visit/end of DDI phase treatment and absolute changes from baseline.
- Shift tables using CTCAE grades to compare baseline to Day 28 Visit.

All LVEF assessments will be listed.

3.3.6 Vital Signs

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

Table 3-2 Criteria for Notable Vital Sign Values

Vital sign	Criteria for clinically notable vital sign values
Systolic blood pressure [mmHg]	≥160 mmHg/≤90 mmHg with increase/decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]	≥100 mmHg/≤50 mmHg with increase/decrease from baseline of ≥15 mmHg
Pulse rate [bpm]	≥120 bpm/≤50 bpm with increase/decrease from baseline of ≥15 bpm
Temperature [°C]	Arms 1 and 3: ≥37.5°C/≤35°C; Arms 2: ≥37.5°C/≤36°C
Weight [kg]	≥20% decrease/≥10% increase from baseline

Descriptive statistics will be provided for baseline, for worst post-baseline value (lowest/highest value) and change from baseline to worst post-baseline value (change from baseline to lowest/highest value) for each vital sign measure.

Frequency counts and percentages of patients having notable vital sign values according to Table 3-2 will be summarized. Clinically notable vital sign values will be flagged in the listings.

3.3.7 Laboratory Data

For laboratory tests covered by CTCAE, Version 4.03, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. If the value is graded ≥1 but falls within the normal range (NR), the grade will be reset to 0. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

Values entered as "<x" or ">x", where x is a numerical value, will be considered as x for the analysis.

The following by-treatment summaries will be generated separately for hematology, biochemistry, and urinary laboratory tests:

- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Incidence of clinically notable shifts in laboratory parameters based on CTCAE grade for specific laboratory evaluations will be summarized, where clinically notable is defined as worsening from baseline by at least 2 grades or to ≥ Grade 3.
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.
- Urinalysis results including appearance, color, specific gravity, pH, ketones, protein, glucose, blood, nitrates, leukocyte esterase, and urine microscopy results including WBC, RBC, epithelial cells, and casts, will be listed.

Table 3-3 and Table 3-4 list all laboratory parameters that will be summarized.

Table 3-3 Laboratory Parameters and Directions for which CTCAE Grades are Defined

Hematology and coagulation		Biochemistry	
White Blood Cells (WBC)	↑↓	Creatinine	↑
Hemoglobin	↑↓	Glucose	↑↓
Platelets counts	↓	Magnesium	↑↓
Neutrophils	↓	Albumin	↓
Lymphocytes	↑↓	AST	↑
Prothrombin Intl. Normalized Ratio	↑	ALT	↑
Activated Partial Thromboplastin Time	↑	Total Bilirubin	↑
		Direct bilirubin (if total bilirubin values are abnormal)	↑
		Amylase	↑
		Lipase	↑
		GGT	↑
		Creatinine phosphokinase/CK	↑
		Alkaline phosphatase	↑

Table 3-4 Laboratory Parameters (without CTCAE Grades) for which Laboratory Reference Ranges are Defined

Hematology and Coagulation	Biochemistry
RBC	BUN
Hematocrit	Calcium
Basophils	LDH
Eosinophils	Bicarbonate
Monocytes	Chloride
Prothrombin Time	

3.3.8 Pregnancy Test

A listing will be produced for the urine and serum pregnancy test and will include all female patients regardless of test result.

3.4 Pharmacokinetics and CCI

3.4.1 Pharmacokinetics

3.4.1.1 Plasma Concentration

Blood samples for PK assessments of midazolam and its metabolite (1-hydroxymidazolam, free [unconjugated] and total [unconjugated and glucuronide conjugated]), caffeine and its metabolite (paraxanthine), omeprazole and its metabolite (5-hydroxy omeprazole), rosuvastatin, bupropion and its metabolite (hydroxybupropion), encorafenib and its metabolite (LHY746), and binimetinib and its metabolite (AR00426032), will be collected from all patients on Days -7, 1, 14 and 21 (as appropriate) at the following time points: predose, and 1, 2, 3, 4, 6 and 8 hours postdose.

Plasma concentrations of free (unconjugated) and total (unconjugated and glucuronide conjugated) 1-hydroxymidazolam will be determined in Arm 1 patients using validated assays. Plasma concentrations of glucuronide conjugated 1-hydroxymidazolam will be derived as below:

glucuronide conjugated 1-hydroxymidazolam = total 1-hydroxymidazolam – free 1-hydroxymidazolam.

Where glucuronide conjugated 1-hydroxymidazolam derived concentrations are negative, these will be treated as below the limit of quantification (BLQ) and set to zero.

Plasma concentrations of each analyte mentioned above will be summarized over scheduled time points by arm and study day using the following descriptive statistics: number of observations (n), number on non-zero observations (m), mean, SD, geometric mean, CV, geometric CV, median, minimum and maximum. In addition, plasma concentrations of rosuvastatin, encorafenib and its metabolite (LHY746), and binimetinib and its metabolite (AR00426032) in Arm 2 will be summarized over scheduled time points by race (non-Asian and overall). Dose normalization may be used where appropriate for summarization of plasma concentration data. Individual plasma concentration of each analyte will be presented in data listings. Data from patients excluded from the PK Set will be presented in the data listings but

not included in the calculation of summary statistics. Concentrations below the lower limit of quantitation (LLOQ) will be treated as zero and will be displayed in the listings as zero and flagged. Missing values of concentrations will not be imputed and will be excluded from the calculations.

Mean and individual concentration-time profiles for each analyte will be presented in figures on linear and semi-logarithmic scales for each arm and study day.

3.4.1.1.1 Caffeine Plasma Concentration

The protocol states, "During the DDI phase of the study, drinks and food containing caffeine must be excluded 48 hours before PK assessments and the day of PK assessments (i.e., Days -9 to -7, -2 to 1, and 12 to 14)." But there are multiple unobvious dietary sources of caffeine beyond coffee and tea that may be difficult for patients to avoid (e.g., multiple types of soda, chocolate in cookies, pudding, hot chocolate and baked goods, and even decaffeinated coffee can have significant levels of caffeine). Therefore, the caffeine PK data will be examined for obvious deviations, based on comparison with historical caffeine PK data. Clear deviations will be defined as:

- Predose caffeine concentration >1000 ng/mL. In one study, the observed C_{max} after a 100-mg caffeine dose taken in coffee was 1335 ng/mL (Bosilkovska 2014). Predose values greater than 1000 ng/mL would be observed after a 48-hour washout only with dietary caffeine intake during the washout period.
- Caffeine C_{max} that takes place at T_{last}. Caffeine has relatively quick absorption (Nehlig 2018), and so a C_{max} at 8 hours is clear evidence that the patient had dietary caffeine during the PK day.

If a patient has a caffeine PK profile that meets either of these 2 criteria on any PK day, that patient's caffeine and its metabolite paraxanthine data will not be included in the Evaluable PK Set, and the affected profile(s) will not be included in the PK Set.

Caffeine has variable PK with CYP1A2 gene polymorphism and other factors contributing to interindividual differences (Nehlig 2018). Variations in the half-life of caffeine from 2.3 to 9.9 hours have been reported (Blanchard and Sawers 1983). If a patient has quantifiable caffeine in their plasma sample predose, the most likely explanation is that they had improper intake of dietary caffeine during the washout period. For a typical half-life of caffeine of 5-6 hours, a 2-day washout should be sufficient for caffeine concentrations to decrease below the LLOQ (25 ng/mL). However, if a patient has a longer half-life (e.g., 10 hours or longer), they may have detectable caffeine levels at baseline. Therefore, the following criterion has been proposed to identify patients that probably had dietary intake of caffeine:

- Predose caffeine concentration >150 ng/mL. The C_{max} from about 2 cups of coffee (estimated 200-mg dose) is expected to be about 2700 ng/mL (based on dose-normalization from the observed 1335 ng/mL from a 100-mg dose) (Bosilkovska et al. 2014). A patient with a $t_{1/2}$ of about 11.5 hours (on the high end of $t_{1/2}$ value range for caffeine) that drank 2 cups of coffee directly before the 48-hour washout period may have a predose caffeine plasma concentration of about 150 ng/mL (i.e., calculated as $2700 \times \exp[-0.693 \times 48 \text{ hours} / 11.5 \text{ hours}]$). Therefore, a predose value >150 ng/mL

suggests the patient had improper dietary intake of caffeine during the 48-hour washout period.

Data from a patient caffeine PK profile with a predose caffeine plasma concentration >150 ng/mL but <1000 ng/mL on any PK day will be flagged in the concentration listings but included in summarization with the PK Set. However, a patient's caffeine and its metabolite paraxanthine data will be excluded from the Evaluable PK Set if their predose caffeine plasma concentration is >150 ng/mL on any PK day.

3.4.1.2 Plasma Pharmacokinetic Parameters

For the calculation of PK parameters, all plasma concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that occur between measurable plasma concentrations or after C_{max} will be set to missing.

The following plasma PK parameters will be calculated on Days -7, 1, 14, and 21, as appropriate, by non-compartmental methods using Phoenix® WinNonlin® Version 8.0 or higher (Certara USA, Inc., Princeton, New Jersey). All calculations will be based on actual sampling times.

Parameter	Definition
C_{max}	maximum observed plasma concentration
AUC_{last}	area under the concentration time curve (AUC) from time zero to the time of last quantifiable concentration, calculated using the linear trapezoidal/linear interpolation method
AUC_{inf}	AUC from time zero extrapolated to infinity (following single administration only)
$AUC_{\%extrap}$	percent of AUC extrapolated (following single administration only)
T_{max}	time to reach maximum observed plasma concentration
Kel	apparent terminal elimination rate constant
$T_{1/2}$	terminal elimination half-life, calculated as: ln(2) / Kel Note: r^2 needs to be $\geq$0.8 to retain Kel and its related PK parameters, and C_{max} must not be included in the calculation.
CL/F	apparent total body clearance of drug from the plasma (parent drugs only), calculated as: Dose / AUC_{inf} (single administration) Dose / AUC_{last} (repeated administration)
V_z/F	apparent volume of distribution during the terminal phase (parent drugs only), calculated as: CL/F / Kel
$MR_{AUClast}$	ratio of AUC_{last} values of the metabolite compared to parent, corrected for molecular weight (for 1-hydroxymidazolam/midazolam, paraxanthine/caffeine, 5-hydroxyomeprazole/omeprazole, bupropion/hydroxybupropion, LHY746/encorafenib, and AR00426032/binimetinib)
MR_{AUCinf}	ratio of AUC_{inf} values of the metabolite compared to parent, corrected for molecular weight (for 1-hydroxymidazolam/midazolam, paraxanthine/caffeine, 5-hydroxyomeprazole/omeprazole, bupropion/hydroxybupropion, LHY746/encorafenib, and AR00426032/binimetinib)
MR_{Cmax}	ratio of C_{max} values of the metabolite compared to parent, corrected for molecular weight (for 1-hydroxymidazolam/midazolam, paraxanthine/caffeine, 5-hydroxyomeprazole/omeprazole, bupropion/hydroxybupropion, LHY746/encorafenib, and AR00426032/binimetinib)
$AR_{AUClast}$	accumulation ratio for encorafenib and its metabolite LHY746, and binimetinib and its metabolite AR00426032, based on AUC_{last}, calculated as: AUC_{last} (Day 14) / AUC_{last} (Day 1), for Arm 1 and Arm 2 only

AR_{Cmax} accumulation ratio for encorafenib and its metabolite LHY746, and binimetinib and its metabolite AR00426032, based on C_{max}, calculated as: C_{max} (Day 14) / C_{max} (Day 1), for Arm 1 and Arm 2 only

The PK parameters for each analyte will be presented in data listings and summarized by arm and study day using the following descriptive statistics: n, mean, SD, geometric mean, CV, geometric CV, median, minimum, and maximum. In addition, PK parameters of rosuvastatin, encorafenib and its metabolite (LHY746), and binimetinib and its metabolite (AR00426032) in Arm 2 will be summarized over study day by race (non-Asian and overall). For T_{max} only n, median, minimum, and maximum will be presented. Dose normalization may be used where appropriate for summarization of PK parameters. If $AUC_{\%extrap}$ is >20%, AUC_{inf} will be listed but not be included in summary statistics or statistical analysis.

If appropriate, PK parameters for encorafenib, LHY746, binimetinib, and AR00426032 in Arms 2 and 3 may be summarized by smoking status and presented in a table.

3.4.1.2.1 Caffeine Pharmacokinetic Parameters

Due to the issues described in Section 3.4.1.1.1 relating to dietary caffeine intake, if a patient has a caffeine PK profile that meets the following criteria on any PK day, the affected profile will be flagged in the parameter listings and included in the summarization and statistical analysis of caffeine parameters with the PK Set:

- Predose caffeine plasma concentration >150 ng/mL but <1000 ng/mL

If a patient has a caffeine PK profile that meets either criteria stated below on any PK day, PK parameters for that profile will be included the parameter listing; however, the affected profile of caffeine and its metabolite paraxanthine will be excluded from all data summarization and statistical analysis:

- Predose caffeine concentration >1000 ng/mL
- Caffeine C_{max} that takes place at T_{last}

Additionally, PK parameters will also be calculated based on baseline-adjusted caffeine concentrations for all profiles, regardless of the predose level. Baseline-adjusted concentrations will be calculated as follows:

> Baseline adjusted concentration = measured concentration – [predose concentration * e^{-Kel*t}], where Kel is terminal elimination rate constant based on actual measured concentration values for each profile and t is the actual sampling time.

Where patients do not have a quantifiable caffeine predose concentration (i.e., predose = BLQ), unadjusted caffeine data will be carried over and used in baseline-adjusted tables, listings, and figures (TLFs), on the assumption that BLQ = zero; hence, baseline adjusting all concentrations by a factor of zero would be equivalent to the unadjusted data. For example, if a patient has a quantifiable predose value on only 1 or 2 of their PK days, and on the other day(s) the predose is BLQ, all 3 days will be used in the baseline-adjusted analysis.

Baseline-adjusted concentrations will be listed and summarized. If a patient has a caffeine PK profile that meets the criterion stated below on any PK day, baseline-adjusted parameters for that profile will be flagged in the listings; however, the patient will be excluded from all data summarization using Evaluable PK Set and PK Set.

- Caffeine C_{max} that takes place at T_{last}

3.4.1.3 Urine Concentration

In Arm 1 only, urine samples will be collected predose and 0 to 8 hours after dosing on Days -7, 1 and 14. The individual patient urine collection volume (Vol) from 0 to 8 hours on Days -7, 1 and 14 and concentrations for losartan and its metabolite (E-3174), and dextromethorphan and its metabolite (dextrorphan), will be presented in listings.

3.4.1.4 Urine Pharmacokinetic Parameters

PK parameters of losartan, E-3174, dextromethorphan and dextrorphan will be computed from the individual patient urine concentrations and collection volumes on Days -7, 1 and 14.

PK parameters will be calculated as follows:

Ae_{0-8}	amount excreted into the urine over the collection interval of 0 to 8 hours. Ae_{0-8} is equivalent to $[CumA]_e$ used in protocol
MR_{Ae0-8}	ratio of Ae_{0-8} values of the metabolite compared to parent, corrected for molecular weight (E-3174/losartan, and dextrorphan/dextromethorphan)
Fe	percentage of dose recovered in urine from 0 to 8 hours as parent or metabolite, calculated as Ae_{0-8} / dose × 100 (metabolite data will be adjusted to account for molecular weight)

The individual urine PK parameters will be presented in listings and summarized separately using the following descriptive statistics for each study day: n, mean, SD, geometric mean, CV, geometric CV, median, minimum, and maximum.

For losartan and its metabolite E-3174 only, dose normalized parameters will be calculated and reported as patients received 50 mg losartan per earlier versions of protocol (prior to Version 5.0) but will receive 25 mg of losartan per protocol Version 5.0. and later versions.

3.4.1.5 Statistical Analysis of Plasma and Urine Pharmacokinetic Parameters

For the primary analysis in Arms 1 and 2, an analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed C_{max}, AUC_{last}, and AUC_{inf} of midazolam, 1-hydroxymidazolam, caffeine and baseline-adjusted caffeine, paraxanthine, omeprazole, 5-hydroxyomeprazole, rosuvastatin, bupropion, and hydroxybupropion in plasma and performed on natural log (ln)-transformed Ae_{0-8} of of losartan, E-3174, dextromethorphan, and dextrorphan in urine (dose normalized parameters for losartan and E-3174). In addition, the analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed C_{max}, AUC_{last}, and AUC_{inf} PK parameters of rosuvastatin, encorafenib and its metabolite (LHY746), and binimetinib and its metabolite (AR00426032) in Arm 2 by race (non-Asian and overall). For the primary analysis in Arm 3, an ANOVA will be performed on the encorafenib, LHY746, binimetinib, and AR00426032 (ln)-transformed C_{max}, AUC_{last}, and AUC_{inf}. The ANOVA model will include day as fixed effect and patient as the random effect. Each ANOVA will include

calculation of least squares means (LSM), the difference between LSM for each day, and the standard error associated with this difference. Ratios of LSM will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the (ln)-transformed parameters. In Arms 1 and 2, these ratios will be expressed as a percentage of Day 1 (test) relative to Day -7 (reference), Day 14 (test) relative to Day 1 (reference), and Day 14 (test) relative to Day -7 (reference). In Arm 3, these ratios will be expressed as a percentage of Day 21 (test) relative to Day 14 (reference).

The statistical analysis will only include patients where each parameter of interest is available for all 3 PK occasions.

Consistent with the 2 one-sided test, 90% confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between LSM resulting from the analyses on the (ln)-transformed parameters.

Similarly, an ANOVA will be performed on the (ln)-transformed $MR_{AUClast}$, MR_{AUCinf}, and MR_{Cmax} calculated for 1-hydroxymidazolam/midazolam, paraxanthine/caffeine, 5-hydroxyomeprazole/omeprazole, hydroxybupropion/bupropion, LHY746/encorafenib, and AR00426032/binimetinib, and MRAe0-8 for E-3174/losartan and dextrorphan/dextromethorphan.

Geometric mean ratios and corresponding 90% CIs of PK parameters in plasma (C_{max}, AUC_{last}, and AUC_{inf}, MR_{Cmax}, $MR_{AUClast}$, and MR_{AUCinf} for metabolites) and urine (Ae_{0-8}) will be presented in forest plots to allow for an overview effect of encorafenib and binimetinib on CYP probe cocktail or rosuvastatin (Arms 1 and 2) or effect of modafinil on encorafenib and binimetinib (Arm 3).

In addition, plots of individual PK parameters (C_{max}, AUC_{last} and AUC_{inf}, Ae_{0-8}) and, where applicable, metabolite to parent AUC and C_{max} ratios combined with corresponding geometric means will be provided versus treatment for Arms 1 and 2 (probe substrates and metabolites) and Arm 3 (encorafenib, LHY746, binimetinib, and AR00426032).

CCI [redacted]

3.5 Other Analysis

Interim analyses may be conducted after a sufficient number of patients have completed Day 28 Visit (i.e., reached end of DDI phase) in each arm. A full analysis for Arm 2 will be conducted when all patients in this arm complete the DDI phase. This full analysis may be repeated for Arms 1 and 3 separately or combined, based on the timing of all patients in the

respective arms completing the DDI phase. A final analysis will be done when all patients have completed the study.

After final database lock, another full database transfer, including all Study Data Tabulation Models (SDTM), Analysis Data Models (ADaM), PK, and safety TLFs will be performed.

Furthermore, the individual lesion measurements and best overall response during treatment evaluated at the end of study will be listed and summarized by tumor type.

4 Data reported in the unscheduled visit forms of the eCRFs will be listed only in the final supplemental CSR for the Post-DDI Phase.Changes from the Analysis Described in the Protocol

4.1 Caffeine Dose

Per protocol, patients enrolled in Arm 1 of the study were scheduled to receive a single dose of 100 mg caffeine as a part of CYP probe cocktail on Days -7, 1 and 14; however, patients in the study received the salt form of caffeine (caffeine citrate), which equates to 50 mg caffeine in free-base form. The data from the first 3 patients who inadvertently received the lower dose of caffeine showed that there is adequate bioanalytical quantification at the 50 mg free-base dose level to support the evaluation of the primary objective of the study. The protocol was therefore updated to amend the caffeine dose to 50 mg free base in Arm 1 of the study in Amendment 5. All caffeine PK parameters will be based on 50 mg free-base dose level.

5 Changes to the Statistical Analysis Plan

Version 2 is an update to Version 1.0 of SAP- Detailed Statistical Methodology.

This incorporates the changes made as of Version 7 of the Protocol. Major changes in Version 2.0 includes:

- Sample size of patient enrollment is included in description of Arms as per study design in Section 2.2.1.
- Details of subject exclusion criteria is added in Pharmacokinetic Section 2.4.2 of analysis sets.
- Added Section 2.9 for subgroup analyses.
- Section for Hydroxymidazolam Plasma Concentration is removed, and the corresponding text is moved to Plasma Concentration under Section 3.4.1.1.
- Added a sentence to clarify that Arm 2 will be summarized over scheduled time points by race (non-Asian and overall) under Section 3.4.1.1.
- Additional analysis of PK Parameter which includes Rosuvastatin, Encorafenib and its metabolite (LHY746), and Binimetinib and its metabolite (AR00426032) in Arm 2 will be analyzed by race under Section 3.4.1.2.

- Dose normalization and analysis methodology for PK parameters is added in Section 3.4.1.5.
- Updated details on interim analyses under Section 3.5.

Version 3.0 is an update to Version 2.0 of SAP- Detailed Statistical Methodology.

This incorporates the changes made as of Version 8.0 of the Protocol. Major changes in Version 3.0 includes:

- The DDI Phase has been defined in Section 2.2.1;
- Derivations of dosing parameters have been revised in Sections 2.5.2 through 2.5.4;
- The dose reduction definition has been revised in Section 2.5.5;
- Added a summary of tumor types and stages in Section 3.2.5 and a summary for best overall responses in Section 3.5;
- Urinalysis shift tables have been removed from Tables 3-3 and 3-4;
- The list of urinalysis results was updated in Section 3.3.7.

A summary of major changes from Version 3.0 of the SAP to Version 4.0 include:

- All enrolled set has been added, it includes all patients who receive at least one dose of any study drug (Safety set as per Version 3.0).
- Safety set has been updated, it will include patients who receive at least one dose of encorafenib/binimetinib.
- Additional summary has been included for Arm 1 under Section 3.2.2.
- As per 'Protocol Administrative Change Letter (PACL)', all AE data is collected in post-DDI phase hence it has been updated at all required places within SAP.
- TEAE derivation has been updated under Section 3.3.1.

A summary of major changes from Version 4.0 of the SAP to Version 5.0 include:

- The definition of Study Day 1 in Section 3.1.1 was updated for cases when patients do not receive encorafenib/binimetinib.
- The lower limit for temperature in the Criteria for Notable Vital Sign Values table in Section 3.3.6 was revised from 36°C to 35°C for Arms 1 and 3 and 36°C for Arm 2.
- A statement in Section 3.5 was added to list data from unscheduled visits.

6 References

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