



STATISTICAL ANALYSIS PLAN

A Phase 1/2a Open-Label, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Mirdametinib in Combination with BGB-3245 in Patients with Advanced Solid Tumors

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LIST OF ABBREVIATIONS

Abbreviation (ACRONYM)	Definition
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ARAF	A-Raf proto-oncogene serine/threonine kinase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BID	Twice daily
BOIN	Bayesian optimal interval
BOP2	Bayesian optimal interval Phase 2
BRAF	v-Raf murine sarcoma viral oncogene homolog B
BUN	Blood urea nitrogen
CK	Creatine kinase
CKD-EPI	Chronic kidney disease epidemiology collaboration
C _{max}	Maximum concentration
CMC	Cohort management committee
CPK	Creatine phosphokinase
CR	Complete response
CRAF	Raf-1 proto-oncogene serine/threonine kinase (see also RAF1)
CRC	Colorectal cancer
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DBP	Diastolic blood pressure
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EoT	End of treatment
ERK	Extracellular signal-regulated kinase

Abbreviation (ACRONYM)	Definition
FDA	United States Food and Drug Administration
GGT	Gamma-glutamyl transferase
HLGT	High level group term
HLT	High level term
HR	Heart rate
HRAS	Harvey rat sarcoma viral oncogene homolog
IA	Interim analysis
ICF	Informed Consent Form
IF	Immunofluorescence
IHC	Immunohistochemistry
INR	International normalized ratio
KRAS	Kirsten rat sarcoma viral oncogene homolog
LD	Longest diameter
LLT	Lowest level term
LRV	Lower Reference Value
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MAPK1	Mitogen-activated protein kinase 1
MAP2K1	Mitogen-activated protein kinase kinase 1
MAP2K2	Mitogen-activated protein kinase kinase 2
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MEK	Mitogen-activated protein kinase kinase
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NA	Not applicable
NCI	National Cancer Institute
NF1	Neurofibromatosis Type I
NGS	Next generation sequencing
NRAS	Neuroblastoma RAS viral oncogene homolog
NSCLC	Non-small cell lung cancer
OCT	Optical coherence tomography
ORR	Objective response rate
PFS	Progression free survival
PD	Progressive disease
PDx	Pharmacodynamic(s)



Abbreviation (ACRONYM)	Definition
pERK	Phosphorylated ERK
PK	Pharmacokinetic(s)
PoC	Proof of concept
PR	Partial response
PT	Preferred term
QD	Once a day
QTcF	corrected QT interval by the Fridericia formula
RAF1	Raf-1 proto-oncogene serine/threonine kinase (see also CRAF)
RAS	Rat sarcoma virus
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Stable disease
SoA	Schedule of Assessments
SOC	System organ class
Spry	Sprouty proteins
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TTP	Time to progression
TV	Target value
WBC	White blood cell
WHO-DD	World Health Organization-drug dictionary
WOCBP	Women of child-bearing potential



1 INTRODUCTION

This statistical analysis plan (SAP) is based on protocol MEKRAF-AST-101 dated 13 July 2022, protocol amendment 1 dated 22 August 2022, and protocol amendment 2 dated 24 July 2023. The SAP contains a complete and detailed specification of the statistical analyses. No objective responses have been observed at the doses tested in Part 1 of the study and dose limiting toxicities (DLTs) prohibited further dose escalation with continuous dosing of both agents. Thus, the sponsor has decided to stop further enrollment in Part 1 of the study and proceed to close the study in 2024. As a result, Part 2 analyses will no longer be done. In addition, efficacy related analyses will be abbreviated due to lack of clinical benefit. This SAP has been updated to reflect the study's premature closure on the planned analyses.

1.1 Rationale

Multiple therapies targeting the v-RAF murine sarcoma viral oncogene homolog B (BRAF) kinase have been approved by the United States Food and Drug Administration (FDA) as single agents and in combination with mitogen activated protein kinase kinase (MEK) inhibitors for patients with Class I BRAF mutations, including those mutations found in melanoma and non-small cell lung cancer (NSCLC). Class I BRAF mutations activate the mitogen activated protein kinase (MAPK) pathway via a BRAF monomer. However, this approach provides no benefit for patients with BRAF Class II or BRAF Class III mutations that require BRAF dimers for activation. In addition, tumors that harbor rat sarcoma virus (RAS) mutations form heterodimers with other members of the RAF family of kinases, Raf-1 proto-oncogene and serine/threonine kinase (RAF1 [also called CRAF]), and A-Raf proto-oncogene serine/threonine kinase (ARAF) to activate the MAPK pathway. To address BRAF dimerization, a new class of pan-RAF inhibitors has been developed to be studied as monotherapy or in combinations.

Novel combinations of MEK inhibitors coupled with these pan-RAF dimer inhibitors are being investigated to address RAS mutant tumors that occur in ~20% of all human cancers. The therapeutic strategy for this combination focuses on maximizing inhibition of MEK phosphorylation with a MEK inhibitor and MAPK pathway activation and with a pan-RAF inhibitor. The intention is to reduce phosphorylated extracellular signal-regulated kinase (pERK) and inhibit feedback loops that increase MAPK signaling, both achieved by directly reactivating the MAPK pathway (e.g., DUSP6). The combination also removes negative regulators of RTK signaling (e.g., Sprouty [Spry] proteins) that can activate RAS and associated downstream pathways. A potential benefit of the synergy attained by this dual inhibition of RAF and MEK is to maximally inhibit the oncogenic pathway and provide more durable antitumor activity.

Mirdametinib (also known as PD-0325901) is an allosteric inhibitor of MEK1 and MEK2 kinases. As a potent MEK inhibitor, mirdametinib significantly inhibits pERK1 and pERK2, neurofibromatosis 1 [NF1], mitogen-activated protein kinase kinase 1 (MAP2K1), mitogen-activated protein kinase kinase 2 (MAP2K2), and mitogen-activated protein kinase 1 (MAPK1).

Brimarafenib (also known as BGB-3245) is a second-generation RAF kinase monomer and dimer inhibitor developed for the treatment of patients with tumors harboring BRAF Class I or BRAF V600 mutations, the BRAF Class II or BRAF non-V600 mutations that are kinase-



activated, BRAF Class III or BRAF non-V600 mutations that are kinase-impaired, or BRAF fusion and splicing variant proteins and other MAPK pathway aberrations that are dependent on RAF monomer or RAF dimer activity. This includes ARAF, RAF1/CRAF, and tumors harboring the mutation of the neuroblastoma RAS viral oncogene homolog (NRAS), Kirsten rat sarcoma viral oncogene homolog (KRAS), or Harvey rat sarcoma viral oncogene homolog (HRAS).

The study MEKRAF-AST-101 sponsored by SpringWorks Therapeutics is a Phase 1/2a study of a pan-RAF inhibitor brimarafenib in combination with a MEK inhibitor mirdametinib in patients with advanced refractory solid cancers harboring MAPK pathway mutation(s) (noted above). This will be the first study to examine brimarafenib in combination with mirdametinib. The main objectives of this study are to evaluate the safety and tolerability of a dose range of each of the combination agents and to assess the clinical anti-tumor activity of the combination agents in participants with advanced, refractory solid tumors that harbor MAPK pathway mutation(s).

2 SUMMARY OF THE PROTOCOL

2.1 Study Objectives

2.1.1 Primary Objective

The primary objectives of the study comprise the following:

- To evaluate the safety and tolerability of mirdametinib and brimarafenib administered as a combination in the eligible participant population (*Part 1 and Part 2*)
- To determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for mirdametinib and brimarafenib administered as a combination in the eligible participant population (*Part 1 only*)
- To determine the preliminary anti-tumor efficacy for the RP2D of mirdametinib and brimarafenib administered as a combination in the eligible participant population (*Part 2 only*).

2.1.2 Secondary Objectives

The secondary objectives of the study comprise the following:

- To determine the preliminary anti-tumor efficacy of mirdametinib and brimarafenib administered as a combination in the eligible participant population (*Part 1 only*)
- To determine duration of response in participants treated with the combination of mirdametinib and brimarafenib (*Part 1 and Part 2*)
- To determine the PK of mirdametinib and brimarafenib administered as a combination in the eligible participant population (*Part 1 and Part 2*).

2.1.3 Exploratory Objectives

The exploratory objectives of the study comprise the following:

- To determine if the combination of mirdametinib and brimarafenib delays disease progression in this participant population (*Part 2 only*)

- To detect tumor mutation/co-mutation status and correlate with anti-tumor activity (Part 1 and Part 2)
- To detect candidate biomarkers of response and to correlate with brimarafenib + mirdametinib exposure (Part 1 and Part 2).

2.2 Study Design

This study is a Phase 1/2a open-label, multicenter, dose-escalation and -expansion study of mirdametinib in combination with brimarafenib in adult patients with histologically confirmed, advanced (American Joint Committee on Cancer (AJCC) Stage III or IV) metastatic or unresectable solid cancer that is refractory to or has progressed during or after at least 1 line of systemic anti-cancer therapy, or for which treatment is not available, or prior standard of care therapy was not tolerated.

The study will be conducted in two sequential parts: Part 1 dose-escalation (Phase 1) and Part 2 dose expansion (Phase 2a). Part 1 of the study will consist of a dose-escalation and dose-finding component to establish the MTD and RP2D and to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PDx) for the combination of mirdametinib with brimarafenib. The planned analysis for PK and PDx endpoints will be described in a separate SAP and will not be part of this SAP. The dose of brimarafenib will start at 5 mg QD and the dose of mirdametinib will start at 2 mg BID. Part 2 will consist of a component to further evaluate the PK, safety, and tolerability of the combination of mirdametinib and brimarafenib at the RP2D, and to assess the preliminary antitumor activity of the combination.

Participants will receive mirdametinib and brimarafenib administered by mouth every day on a continuous schedule. Mirdametinib will be dosed twice a day (BID) and brimarafenib will be dosed once a day (QD), as shown in Table 1. One treatment cycle will be 28 days.

Part 1 of the study was closed early due to the lack of objective responses in the doses tested and the DLTs that prohibited further dose escalation with brimarafenib and mirdametinib in combination. As the MTD of the combination was deemed minimally efficacious, SpringWorks, in consultation with MapKure and the study's Cohort Management Committee, terminated this study. Part 2 of the study was not opened for these reasons. The planned PK and PDx analysis will also be limited and described within this SAP due to the minimal number of samples from the early closure of the study.

2.3 Part 1 (Phase 1 Dose Escalation)

Part 1 is a Phase 1, multicenter, open-label, multiple dose, dose-escalation study in participants with advanced metastatic or unresectable solid tumors harboring an oncogenic mutation or other aberrations of the MAPK pathway. The mutations and aberrations of the MAPK pathway include: a known mutation status and tumor harboring an oncogenic mutation of the v-RAF murine sarcoma viral oncogene homolog B (BRAF) gene (including BRAF Class I or BRAF V600 mutations, the BRAF Class II or BRAF non-V600 mutations that are kinase-activated, BRAF Class III or BRAF non-V600 mutations that are kinase-impaired, or BRAF fusion), A-Raf proto-oncogene serine/threonine kinase [ARAF], and Raf-1 proto-oncogene, serine/threonine kinase [RAF1/CRAF]. In addition, participants with tumors harboring the



mutation of NRAS, KRAS, or HRAS, neurofibromatosis 1 [NF1], mitogen-activated protein kinase kinase 1 [MAP2K1], mitogen-activated protein kinase kinase 2 [MAP2K2], and mitogen-activated protein kinase 1 [MAPK1] are eligible for Part 1.

Participants with CRC or pancreatic cancer that harbor KRAS mutations will be limited to approximately one-third of each cohort (e.g., not to exceed 1 of 3 or 2 of 6 participants per cohort). The Cohort Management Committee (CMC) will evaluate DLTs during the first cycle consisting of the first 28 days of concurrent mirdametininib and brimarafenib treatment.

Cohort management decisions in Part 1 will be governed by the CMC (see Section 12.1 of the protocol). The CMC meeting will be scheduled after at least 3 participants in each dose cohort become evaluable for DLT assessment. If 2 of the first 3 participants have a DLT, the CMC meeting will commence prior to the third participant completing the DLT assessment period as this meets Bayesian Optimal Interval (BOIN) criteria stopping rules. The CMC will consider the BOIN rules and all available data (safety, toxicity modeling and prediction, PK, tumor response) from all participants treated up until the CMC meeting.

Table 1 shows the potential study treatment groups and their respective treatment labels for Part 1 using the primary dose escalation scheme; the alternate dose escalation scheme is shown in Figure 1. Not all treatment groups will be used; only populated groups will be used in outputs. Of note, based on the DLT assessments and in consultation with the CMC, alternative dosing regimens may be used (Figure 1).

Table 1 Planned Study Treatment Groups (Part 1)

Cohort	Actual Treatment	Dose Escalation Plan	Treatment Label
1	2 mg BID mirdametininib + 5 mg QD brimarafenib	Primary	2 mg + 5 mg
2	2 mg BID mirdametininib + 10 mg QD brimarafenib	Primary	2 mg + 10 mg
3	2 mg BID mirdametininib + 20 mg QD brimarafenib	Primary	2 mg + 20 mg
4	2 mg BID mirdametininib + 30 mg QD brimarafenib	Primary	2 mg + 30 mg
5	3 mg BID mirdametininib + 30 mg QD brimarafenib	Primary	3 mg + 30 mg
6	4 mg BID mirdametininib + 30 mg QD brimarafenib	Primary	4 mg + 30 mg



Table 2 shows the actual doses used for the treatment of the cohorts in Part 1 of the study.:

Table 2 Actual Treatment Cohorts in Part 1

Cohort	Actual Treatment	Dose Escalation Plan	Treatment Label
1	2 mg BID mirdametinib + 5 mg QD brimarafenib	Primary	2 mg + 5 mg
2	2 mg BID mirdametinib + 10 mg QD brimarafenib	Primary	2 mg + 10 mg
3	2 mg BID mirdametinib + 20 mg QD brimarafenib	Primary – DLTs indicated this dose was above the MTD	2 mg + 20 mg
4	3 mg BID mirdametinib + 10 mg QD brimarafenib	Alternate due to DLTs in Cohort 3	3 mg + 10 mg
5	4 mg BID mirdametinib + 10 mg QD brimarafenib	Alternate – DLTs indicated this dose was above the MTD	4 mg + 10 mg

Table 3 presents the visit labels that will be used in all output for Part 1. Participants can continue study treatment indefinitely until the investigator determines that study treatment will no longer be used.

Table 3 Study Visits

Visit	Visit Label
Screening	Screening
Cycle 1 – Week 1 (Baseline, study visit day 1)	C1D1
Cycle 1 – Week 2 (Cycle Day 8 ±1)	C1D8
Cycle 1 – Week 3 (Cycle Day 15 ±2)	C1D15
Cycle 1 – Week 4 (Cycle Day 22 ±2)	C1D22
Cycle 2 – Week 5 (Cycle Day 1 ±2)	C2D1
Cycle 2 – Week 7 (Cycle Day 15 ±2)	C2D15
Cycle 3 – Week 9 (Cycle Day 1 ±2)	C3D1
Cycle 4 – Week 13 (Cycle Day 1 ±2)	C4D1
Cycle 5 – Week 17 (Cycle Day 1 ±2)	C5D1
Cycle 6 – Week 21 (Cycle Day 1 ±2)	C6D1
Cycle 7 – Week 25 (Cycle Day 1 ±2)	C7D1
Cycle 8 – Week 29 (Cycle Day 1 ±2)	C8D1
Cycle 9 – Week 33 (Cycle Day 1 ±2)	C9D1
Cycle 10 – Week 37 (Cycle Day 1 ±2)	C10D1
Cycle 11 – Week 41 (Cycle Day 1 ±2)	C11D1
Cycle 12 – Week 45 (Cycle Day 1 ±2)	C12D1
Cycle 13 – Week 49 (Cycle Day 1 ±3)	C13D1
Cycle XX – Week 4*(XX-1)+1 (Cycle Day 1 ±3)	CXXD1
End of Treatment	End of Treatment



Visit	Visit Label
Safety Follow-up – 30 ±7 days after last dose	Safety Follow-up
Long-term Follow-up – Every 3 months* ±7 days after last dose	Long-term Follow-up

*Month = 28 days

2.3.1 Starting dose and dose-escalation rules

The planned dose levels of mirdametinib and brimarafenib in Part 1 are shown below in Table 4.

Table 4 Mirdametinib + Brimarafenib Planned Dose Escalation

Cohort	Dosing of mirdametinib	Dosing of brimarafenib (BGB-3245)	Number of evaluable participants
1	2 mg BID	5 mg QD	3 (up to 6)
2	2 mg BID	10 mg QD	3 (up to 6)
3	2 mg BID	20 mg QD	3 (up to 6)
4	2 mg BID	30 mg QD	3 (up to 6)
5	3 mg BID	30 mg QD	3 (up to 6)
6	4 mg BID	30 mg QD	3 (up to 6)

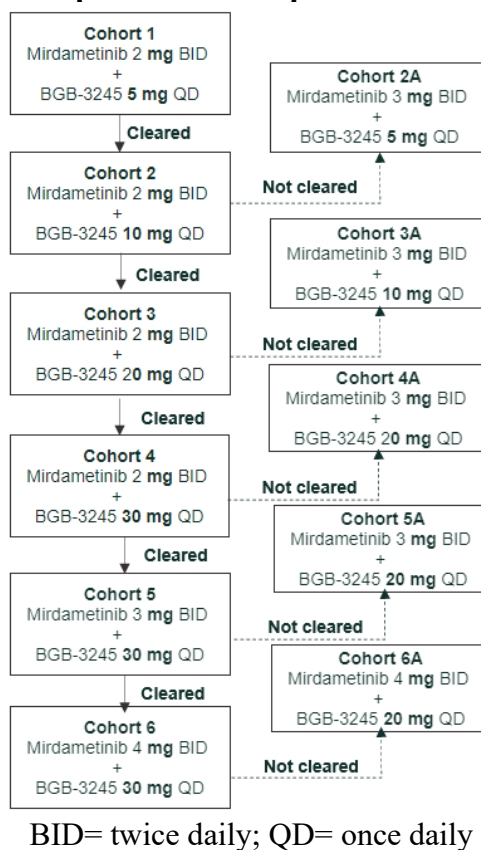
If the highest planned dose level (Cohort 6) is cleared by the CMC based on the BOIN estimate of the toxicity rate and the review of all available data in the study to that point, then the Sponsor in consultation with the CMC may continue dose escalation. The highest doses of mirdametinib will not exceed 8 mg BID and brimarafenib will not exceed 40 mg QD in Part 1.

If a planned dose level is not tolerated based on the BOIN estimate of the toxicity rate derived from the observed DLT rate, an alternate dose exploration could be implemented to identify the optimal dose ratio for the combination of agents. An alternate dose finding scheme may explore lowering of the brimarafenib dose while escalating the mirdametinib dose, see Table 1 and Figure 1. The Sponsor in consultation with the CMC may explore the alternative combination dose ratio based on the review of all available data. A written data summary and interpretation of that data will be prepared by the CMC and the Sponsor to support switching to the alternate dose finding scheme.

In Figure 1 below an alternate dose finding scheme will decrease the dose of brimarafenib while the dose of mirdametinib will be increased. Should this dose level be tolerated based on the BOIN estimate of the toxicity rate described below in the section, doses will be escalated to

achieve the MTD and/or RP2D. Should this dose level not be tolerated, the dose of brimarafenib may be further reduced, if necessary, to a minimum brimarafenib dose of 5 mg. Mirdametinib doses may be increased in 50%-100% increments in the alternate dose exploration but will never exceed 8 mg BID. Brimarafenib doses will not increase above the dose where toxicity was observed to cause the switch to the alternate dose exploration.

Figure 1 Alternate Dose Exploration Examples



During dose escalation, the Sponsor in consultation with the CMC may explore alternative dosing schedules to improve tolerability and facilitate the exploration of the benefit-risk ratio.

2.3.1.1 BOIN Design

The dose escalation will employ the BOIN design to determine the MTD. The target toxicity rate used for the MTD identification is $\phi=0.3$. The BOIN design will use the following rules, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation decisions:

1. Participants in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of participants, conduct dose escalation/de-escalation according to the rule displayed in. When using Table 4, please note the following:
 - a. “Eliminate” means eliminate the current and higher doses from the trial to prevent treating any future participants at these doses because they are overly toxic.



- b. When a dose is eliminated, this will lead to an automatic de-escalation of the dose to the next lower level or an alternate dose level or schedule depending on observed toxicities. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
 - c. If none of the actions (i.e., escalation, de-escalation, or elimination) is triggered, treat the new participants at the current dose.
 - d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new participants at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
 - e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new participants at the highest dose.
3. Repeat step 2 following the BOIN design until the MTD and/or RP2D is determined or stop the dose escalation part if the number of evaluable participants treated at the current dose reaches 6 and the decision according to Table 5 is to stay at the current dose.

Table 5 Dose Escalation/De-Escalation Rule for the BOIN Design

Number of evaluable participants treated at current dose	1	2	3	4	5	6
Escalate if # of DLT \leq	0	0	0	0	1	1
De-escalate if # of DLT \geq	1	1	2	2	2	3
Eliminate if # of DLT \geq	NA	NA	3	3	4	4

Abbreviations: # = number; DLT = dose limiting toxicity; NA = not applicable

NOTE: “# of DLT” is the number of participants with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate, or eliminate) is triggered, stay at the current dose for treating the next cohort of participants. “NA” means that a dose cannot be eliminated before treating 3 evaluable participants.

The dose escalation rules presented in Table 5 correspond to the following rules optimized to minimize the probability of incorrect dose assignment and to guide dose escalation/de-escalation:

- The escalation (lower) boundary is set at 0.236 and the de-escalation (upper) boundary is set at 0.358.
- If the observed DLT rate at the current dose is ≤ 0.236 , escalate the dose to the next higher dose level.
- If the observed DLT rate at the current dose is > 0.359 , deescalate the dose to the next lower dose level.
- If the observed DLT rate at the current dose is > 0.236 and ≤ 0.359 , stay at the current dose.

After the dose escalation is completed, the MTD will be computed using an isotonic regression as specified in Liu and Yuan 2015. The MTD is selected as the dose for which the isotonic estimate of the toxicity rate is less than or equal to 0.359 and closest to the target toxicity rate.



2.3.1.2 Pharmacodynamic (PDx) Expansion Cohort

When the MTD or RP2D has been determined by the Sponsor in consultation with the CMC, then a PDx Expansion Cohort will be initiated. This cohort will consist of a total of 6 to 20 evaluable participants to collect additional biomarker and PDx data. This additional biomarker and PDx data will support the optimization of the RP2D dose.

The participants in the PDx Expansion Cohort must meet the eligibility criteria for participants in Part 1; in addition, the participants in the PDx Expansion Cohort must provide paired fresh tumor biopsies at screening and at Cycle 1 Day 22 (± 2 days). The PDx Expansion Cohort was not opened as the MTD was deemed to be minimally efficacious and the DLTs prevented further dose evaluation.

2.4 Part 2 (Phase 2a Dose Escalation)

Part 2 is a Phase 2a multicenter, open-label dose expansion study in participants with advanced metastatic or unresectable solid tumors harboring the oncogenic mutations specific for each of the expansion cohorts. Part 2 will begin after the RP2D for the combination of mirdametinib and brimarafenib is identified in Part 1. Part 2 may start either in parallel with, or after, the conduct and analysis of the PDx Expansion Cohort in Part 1.

Part 2 will confirm the safety, tolerability, efficacy, PK, and PDx for the combination of mirdametinib and brimarafenib.

Part 2 will follow a parallel design and include one or more dose expansion cohorts, where each participant would be treated with the combination of mirdametinib and brimarafenib at the RP2D.

One or more of the following cohorts may be opened in parallel, or sequentially at the Sponsor's discretion:

- Expansion Cohort A (n=20 evaluable participants): Participants with cutaneous melanoma harboring an NRAS mutation.
 - Minimum of 15 (75%) of the 20 participants in Cohort A must have a NRAS Q61x mutation (i.e., Q61R, Q61K, Q61L).
- Expansion Cohort B (n= 30 evaluable participants): Participants with NSCLC harboring a KRAS mutation
 - Minimum of 15 (50%) of the 30 evaluable participants in Cohort B must have a KRAS G12V mutation.
- Expansion Cohort C (n=30 evaluable participants): Participants with NSCLC or cutaneous melanoma harboring BRAF Class II or Class III mutations or BRAF fusion.
 - Cohort C1: Approximately 15 evaluable participants with NSCLC harboring BRAF Class II or Class III mutations or BRAF fusion.
 - Cohort C2: Approximately 15 evaluable participants with cutaneous melanoma harboring BRAF Class II or Class III mutations or BRAF Fusion.



Additional cohorts of up to 30 evaluable participants each with specific tumor histology and/or mutation status may be included in Part 2 expansion phase, if supported by the efficacy signals observed during the dose escalation phase.

A participant will be evaluable for Part 2 dose expansion cohort if they provide a baseline radiological tumor assessment at the Screening Visit and for at least one time point after the start of study treatment and these assessments allow an evaluation of the tumor response. The first post-treatment tumor assessment after 2 cycles will be used to assess Objective Response Rate (ORR) for decision making at the interim analysis (IA). For the final analysis all post-baseline tumor assessments will be used to assess tumor response status. The final analysis and its implementation schedule will be determined based on the results of the interim analysis, as the current data is insufficient to make a definitive determination. Upon receipt of the interim analysis result, it may be necessary to amend the SAP to define potential changes for the final analysis.

Table 6 below presents the treatment group labels and the visit labels that will be used in all outputs for Part 2. These are the same as in Part 1. Participants can continue treatment until the investigator determines that study treatment will no longer be used or the timepoint for final analysis has been reached.

Table 6 Study Treatment Groups (Part 2)

Expansion Cohort	Tumor Type	Actual Treatment	Treatment Label
A	Cutaneous melanoma harboring NRAS mutations	RP2D of mirdametininib BID + RP2D of brimarafenib QD	Cohort A
B	NSCLC harboring a KRAS mutation	RP2D of mirdametininib BID + RP2D of brimarafenib QD	Cohort B
C	NSCLC or cutaneous melanoma harboring BRAF Class II or Class III mutations or BRAF Fusion mutation	RP2D of mirdametininib BID + RP2D of brimarafenib QD	Cohort C

2.4.1 Interim Analysis

Each of the 3 cohorts will have one interim analysis when 50% of the planned total sample size is evaluable for confirmed ORR and the stopping criteria for futility at interim and final analysis will be applied as described in Table 7 below. These stopping criteria are non-binding but provide guidance for decision making.

Table 7 Stopping Criteria

Cohort	LRV/TV*	Stopping criteria at interim analysis # of responder/# of evaluable	Stopping criteria at final analysis # of responder/# of evaluable	Overall power and 1-sided alpha=0.05
A	15%/40%	$\leq 2/10$	$\leq 5/20$	78%
B	15%/35%	$\leq 3/15$	$\leq 7/30$	78%
C	10%/30%	$\leq 2/15$	$\leq 5/30$	84%

Abbreviations: LRV = Lower Reference Value; TV = Target Value.

*LRV is estimated for each of the cohorts from historical data as expected ORR under standard of care in the respective population.

Once confirmed ORR can be assessed in each of the dose-expansion cohorts (approximately 10 evaluable participants in Cohort A and 15 participants in Cohorts B and C), the Sponsor will conduct an IA of all available safety, efficacy, PK and PDx data, and the stopping criteria following the Bayesian optimal interval Phase 2 (BOP2) design will be assessed (Zhou, Lee, and Yuan 2017). Other efficacy criteria such as duration of response may be considered for the decision at the time of IA. Enrollment may continue in parallel until a decision about the stopping criteria is achieved.

The goal of the IA will be to determine if the anti-tumor efficacy and tolerability of study treatments administered at the RP2D meets the Sponsor's predefined criteria for the clinical proof-of-concept (PoC). If the stopping criteria at the time of the IA are not met, additional participants will be enrolled and the final analysis performed after the total planned number of participants become evaluable in each of the dose expansion cohorts. In addition to the stopping criteria following the BOP2 design, other efficacy endpoints such as duration of response (DOR) will be considered for the conclusion at the time of final analysis.

Based on the results of any of the interim analyses, the study may be continued, modified, or stopped by the Sponsor. The expansion cohorts may be expanded if deemed appropriate by the Sponsor based on the analysis of all available safety, efficacy, PK and PDx data from that cohort and the consultation with the Regulatory Authorities (if applicable).

2.5 Sample Size Determination

2.5.1 Part 1

The planned sample size in Part 1 is up to 56 participants, which includes the following:

- Six dose escalation cohorts (minimum of 3 and up to 6 evaluable participants per cohort;



participant is evaluable if they complete Cycle 1 or experience DLT).

- PDx Expansion Cohort (minimum of 6 and up to 20 evaluable participants).

The planned number of participants in Part 1 may be increased or decreased if deemed necessary by the Sponsor to determine MTD or RP2D.

Participants who are discontinued after the start of treatment in Part 1 (except those discontinued for safety reasons) may be replaced if this is deemed necessary by the Sponsor to accrue enough evaluable participants.

2.5.2 Part 2

Part 2 of the study will be performed after meeting with the FDA to review the results from Part 1. The planned sample size in Part 2 dose escalation is 80 evaluable participants (20 evaluable participants in Cohort A and 30 evaluable participants each in Cohorts B and C). Up to 100 participants may be treated to achieve the planned number of efficacy evaluable participants.

The sample size for the expansion cohorts is based on a BOP2 for each of the cohorts.

2.6 Schedule of Assessments

The full schedule of assessments (SoA) can be found in Sections 1.2-1.4 of the protocol.

3 POPULATIONS FOR ANALYSES

The analysis populations of interest are:

- Safety Population
- DLT Evaluable Population
- Efficacy Evaluable Population
- PK Population

Each of the populations, as well as the criteria for inclusion into each population are described in the following sections.

3.1 Safety Population

The safety population will consist of all participants assigned to study treatment who take at least 1 dose of study treatment (either brimarafenib or mirdametinib).

3.2 DLT Evaluable Population

The DLT evaluable population will include participants who received >80% of the assigned dose of brimarafenib and mirdametinib during Cycle 1 in Part 1 (i.e., at least 23 days on treatment with both study treatments) or who experienced a DLT during Cycle 1 in Part 1.

3.3 Efficacy Evaluable Population

The efficacy evaluable population will include all treated participants who have the baseline tumor response assessment (screening) and at least one post-baseline tumor response assessment. Participants who die before a post-baseline tumor assessment can be performed will be part of the efficacy evaluable population and counted as non-responders.



3.4 PK Population

The PK population will include all treated participants for whom brimarafenib or mirdametinib PK concentrations are measured without major protocol deviations that impact PK concentrations.

4 STUDY MEASURES

This section describes the measures that are collected and/or derived during the study at the time points specified in SoA (Sections 1.2-1.4 of the protocol). This includes efficacy, safety, tolerability, and participant characteristics data.

4.1 Primary Objectives

The primary endpoints described in this section will be analyzed according to the analysis methods described in Section 5.6.

4.1.1 Part 1 and Part 2: Evaluate the safety and tolerability of mirdametinib and brimarafenib administered as a combination in the eligible participant population (Safety Population).

Key safety endpoints will include incidence of Treatment Emergent Adverse Events (TEAEs), changes in clinical laboratory parameters, vital signs, physical examination findings, Eastern Cooperative Oncology Group (ECOG) status, electrocardiograms (ECGs), ophthalmological examinations, and echocardiogram (ECHO)/Multigated Acquisition (MUGA) scan.

TEAEs severities will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

For more information on safety endpoints see Section 4.5.

4.1.2 Part 1 only: Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for mirdametinib and brimarafenib administered as a combination in the eligible participant population.

The MTD, if any, will be based on safety and tolerability during the first 28 days of treatment in Cycle 1.

The RP2D will be determined based on safety, tolerability, PK, preliminary anti-tumor efficacy, and other available data by the Sponsor in consultation with the CMC.

4.1.3 Part 2 only: Determine the preliminary anti-tumor efficacy for the RP2D of mirdametinib and brimarafenib administered as a combination in the eligible participant population (Efficacy Evaluable population).

Anti-tumor efficacy as assessed by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). Objective Response Rate (ORR) defined as the proportion of participants with a confirmed response (complete response (CR) + partial response (PR)), using Response Evaluation Criteria in Solid Tumors (RECIST v1.1; See Appendix 1). To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that will be performed no less than 4 weeks after the criteria for response are first met. To be



assigned a status of SD, changes in tumor measurements must be confirmed for an interval of at least 8 weeks.

Response status is determined by the change in the sum of the longest diameter (LD) of target lesions and the presence/absence of non-target lesions. The baseline value is defined as the last non-missing measurement of target lesions collected prior to the first study treatment administration at C1D1.

The assessment of the anti-tumor efficacy will be based on the central imaging review of scans as well as the investigator assessment of the scans. The central imaging review results will be considered the primary assessment of the anti-tumor efficacy, and the results based on the investigator assessment be considered as supportive. The actual measurements of target lesions (LD for all target lesions and changes from baseline) will be used to confirm the investigator's assessment of response according to RECIST 1.1. criteria.

4.2 Secondary Objectives

The secondary endpoints described in this section will be analyzed according to the analysis methods described in Section 5.7.

4.2.1 Part 1 only: Determine the preliminary anti-tumor efficacy of mirdametinib and brimarafenib administered as a combination in the eligible participant population (Efficacy Evaluable Population).

Anti-tumor efficacy as assessed by CT or MRI. Objective Response Rate (ORR) defined as the proportion of participants with a confirmed response (complete response (CR) + partial response (PR)), using Response Evaluation Criteria in Solid Tumors (RECIST v1.1; See Appendix 1). A confirmed response is defined as in Section 4.1.3.

4.2.2 Part 1 and Part 2: Determine duration of response in participants treated with the combination of mirdametinib and brimarafenib (Efficacy Evaluable Population).

Duration of response, defined as the time from the first instance of confirmed response (CR + PR using RECIST v1.1) to disease progression and/or death.

Duration of response will be derived as the time in months between the first instance of confirmed response (CR or PR, whichever occurs first) using RECIST v1.1 until the date of progression (PD), date of death, or censored date, taking as reference for PD the smallest measurements recorded since the treatment started. Participants who do not experience progression or death will be censored at their most recent assessment showing non-progression of disease. A confirmed response is defined as in Section 4.1.3.

4.3 Exploratory Objectives (Efficacy Evaluable Population)

The exploratory endpoints described in this section will be analyzed according to the analysis methods described in Section 5.8.



4.3.1 Part 2 only: Determine if the combination of mirdametinib and brimarafenib delays disease progression in this participant population.

For each tumor histology in each expansion cohort, estimate of median time-to-progression. Median progression-free survival will also be estimated as a sensitivity analysis.

Time-to-progression (TTP) is derived as the time in months from first study treatment administration at C1D1 until the first date of progression defined as meeting the RECIST v1.1 criteria of Progressive Disease (PD) or death whichever is earlier.

Progression-free survival (PFS) is derived as the time in months from first study treatment administration at C1D1 until the earliest of disease progression, defined as meeting the RECIST v1.1 criteria of Progressive Disease (PD), or death from any cause.

For PFS, participants who do not experience disease progression or death will be censored at their most recent assessment showing non-progression of disease.

4.4 Efficacy Measures

Anti-tumor efficacy as assessed by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). Objective Response Rate (ORR) defined as the proportion of participants with a confirmed response (complete response (CR) + partial response (PR)), using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Based on RECIST v1.1 criteria, CR, PR, SD, and PD will be assessed with the primary focus will be on confirmed responses and SD.

Duration of overall response, defined as the time from first response (CR + PR using RECIST v1.1) to disease progression and/or death.

TTP is derived as the time in months from first study treatment administration at C1D1 until the first date of progression defined as meeting the RECIST v1.1 criteria of PD or death whichever is earlier. Participants who die before progression is observed will be censored at time of death.

PFS is derived as the time in months from first study treatment administration at C1D1 until the earliest of disease progression, defined as meeting the RECIST v1.1 criteria of PD, or death from any cause. Participants who die before progression is observed will be counted as events at time of death.

OS is derived as the time in months from first study treatment administration at C1D1 to death from any cause.

Due to early termination of the study, no formal efficacy analysis will be presented.

4.5 Safety Measures

The safety endpoints described in this section will be analyzed according to the analysis methods described in Sections 5.6.1 (primary objectives) and 5.9 (other safety analyses).

4.5.1 Exposure to Study Treatment

There are multiple dose levels in the study (see Table 4 for Part 1; Part 2 participants to be dosed at RP2D established in Part 1). Participants are dosed continuously with mirdametinib BID and brimarafenib QD. Participants are dosed until the Investigator determines the participant will stop receiving treatment based on benefit-risk assessment, the participant chooses to withdraw, or the study is terminated by the sponsor.

Study treatment may be temporarily interrupted, dose reduced, and/or permanently discontinued in the event of significant TEAEs.

For each participant, the following endpoints will be derived:

- Duration of Treatment
- Did participant receive all planned doses?
- Did participant have any dose modifications?
- Cumulative dose of mirdametinib taken over the course of the study
- Average and median daily dose of mirdametinib
- Cumulative dose of brimarafenib taken over the course of the study
- Average and median daily dose of brimarafenib
- Relative Dose Intensity of mirdametinib
- Relative Dose Intensity of brimarafenib

4.5.2 Adverse Events

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

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Adverse events data are collected from the time of informed consent to 30 days after the last dose of study treatment at the timepoints specified in the SoA (Sections 1.2-1.4 of the protocol).

Missing AE data will not be imputed as stated in Section 4.10.

4.5.2.1 Adverse Event Definitions

Adverse events reported from the time of informed consent until the Safety Follow-up Visit (30 \pm 7 days after the last dose of study treatment) will be recorded as part of the study.

A treatment-emergent adverse event (TEAE) is defined as an AE that occurred or increased in severity after the first dose of study treatment was taken.

A treatment-emergent serious adverse event (TESAE) is defined as a SAE occurring or increasing in severity after the first dose of study treatment was taken and including SAEs occurring up to the Safety Follow-up Visit.



Certain adverse events are specified as adverse events of special interest (AESI). The adverse events that qualify as such are stated in Section 10.4.6 of the protocol.

An AE will be classified as related to study treatment if the relationship to study treatment is recorded (on the 'Adverse Events' CRF page,) as 'Related'. An AE will be classified as unrelated to study treatment if the relationship to study treatment is recorded as 'Not Related'. If the AE's relationship to study treatment cannot be determined, then the relationship to study treatment is recorded as 'Unknown'. Relationship to study treatment is assessed separately for mirdametinib and for brimarafenib. Relationship to study procedure will also be assessed in the same way.

The severity of all AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. For AEs not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- CTCAE Grade 2 Moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- CTCAE Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- CTCAE Grade 4 Life-threatening consequences; urgent treatment indicated.
- CTCAE Grade 5 Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

An AE leading to study discontinuation will be defined as an AE where the response to 'Primary Reason for Discontinuing the Treatment Period' is 'Removal From Study' or 'Withdrawal of Consent', and the response to 'If Removal from Study, specify' or 'If Withdrawal of Consent, specify' is 'Adverse Event'.

An AE leading to treatment discontinuation is defined as an AE where the response to 'Action Taken with mirdametinib' or 'Action Taken with brimarafenib' is recorded as 'Drug Withdrawn' (on the 'Adverse Events' CRF page).

4.5.2.2 Coding of Adverse Event Terms

The AE term (Investigator term) will be assigned to the lowest level term (LLT), and a preferred term (PT) will be classified by a high level term (HLT), a high level group term (HLGT) and a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, Version 27.1 or higher, depending on the latest version available during the study.

Although there can be multiple SOC's for a PT, each PT will be linked with one SOC, namely the primary SOC which is automatically assigned by MedDRA via one HLT, HLGT route.

The following coding data will be presented:

- LLT (Investigator term)
- PT
- Coding data per primary SOC:
 - HLT
 - HLGT

If no coding information is available for a specific AE, the AE will be presented as an 'Uncodable Event' in all summary tables.

Adverse events will be reported on a per participant basis and per event. On a per participant basis means that even if a participant reported the same event repeatedly (i.e., events mapped to the same PT) during the study period, the event will be counted only once. In the latter case the event will be assigned the worst severity and the strongest relationship to the study treatment. The earliest date will be regarded as the start date of the event and the latest date/time will be regarded as the stop date of the event within the assigned study period.

4.5.3 Clinical Laboratory Evaluations

Chemistry and hematology evaluations are performed by local laboratories at Screening, C1D1, C1D8, C1D15, pre-dose C1D22 and C2D1, C2D15, and Day 1 of every cycle thereafter, as well as EoT and Safety Follow-up Visit in accordance with the SoA (Sections 1.2-1.4 of the protocol). Urinalysis evaluations are performed at Screening, Day 1 of Cycles 1-13 and every 3 cycles thereafter, as well as EoT and Safety Follow-up Visit in accordance with the SoA. Coagulation and thyroid function test evaluations are performed at Screening, Day 1 of Cycle 3 and every 2 cycles thereafter until Cycle 13, and then Day 1 of every 3 cycles thereafter, as well as EoT in accordance with the SoA.

All laboratory results are standardized to Système International (SI) units.

Table 8 presents the quantitative and qualitative laboratory tests that are performed.

Table 8 Laboratory Tests

Laboratory Test (Unit)		
Hematology	Serum Chemistry	Urinalysis
WBC (10 ⁹ /L)	Albumin (g/L)	Appearance (N/A)
Neutrophils# (10 ⁹ /L)	Amylase (ukat/L)	Color (N/A)
Basophils# (10 ⁹ /L)	Alkaline phosphatase (U/L)	pH (N/A)
Eosinophils# (10 ⁹ /L)	ALT (U/L)	Specific gravity (N/A)
Lymphocytes# (10 ⁹ /L)	AST (U/L)	Ketones (N/A)
Monocytes# (10 ⁹ /L)	Bicarbonate (mmol/L)	Leukocytes (N/A)
Hemoglobin (g/L)	BUN or equivalent [uric acid, urate] (mmol/L)	Protein (N/A)
Hematocrit (L/L)	Calcium (mmol/L)	Glucose (N/A)
Platelet count (10 ⁹ /L)	Chloride (mmol/L)	Bilirubin (N/A)
MCV (fL)	CK/CPK (U/L)**	Urobilinogen (N/A)
Reticulocytes (%)	Creatinine (umol/L)	Myoglobin or blood**
		Occult blood (N/A)
	eGFR (CKD-EPI calculation)* (mL/min/1.73 m ²)	
Coagulation	GGT (U/L)	Hormones
INR (N/A)	Glucose (fasting or random) (mmol/L)	βHGC (WOCBP only)
aPTT (s)	Glycosylated hemoglobin (HbA1c)* (%)	TSH (uLU/mL)
	Magnesium (mmol/L)	Free T3 (pmol/L)
Lipid panel	Phosphorous (mmol/L)	Free T4 (pmol/L)
Total cholesterol* (mmol/L)	Potassium (mmol/L)	
Triglycerides* (mmol/L)	Sodium (mmol/L)	
	Total bilirubin^ (umol/L)	
	Total protein (g/L)	

Abbreviations: ALT = Alanine Aminotransferase; aPTT = Activated Partial Thromboplastin Time; AST = Aspartate Aminotransferase; βHGC = Beta Human Chorionic Gonadotropin; BUN = Blood Urea Nitrogen; CK = Creatine Kinase; CPK = Creatine phosphokinase; eGFR = estimated Glomerular Filtration Rate; GGT = Gamma-glutamyl Transferase; INR = International Normalized Ratio; MCV = Mean Corpuscular Volume; TSH = Thyroid Stimulating Hormone; WBC = White Blood Cells

* At Screening only to establish eligibility and/or baseline and permit full investigation of clinical observations on study.

** For Grade 3 or higher CK/CPK elevations, it is recommended to monitor and measure isozymes (CPK1, 2, and 3). Evaluation for presence of myoglobin with blood test or with urinalysis is also recommended.

Both the absolute number and proportion (%) should be reported for 5-part WBC differential count.

^ If total bilirubin elevated, conduct direct and indirect bilirubin on subsequent samples.



Descriptive statistics will be provided for each parameter, for actual values and for change from baseline by cohort, and cohorts combined and by visits for continuous variables, count, and frequency will be provided for categorical variables. Multiple measurements taken during the same visit for a participant will be represented by the value taken closest to the target scheduled visit date/time. If same distance, last value will be used. The value of unscheduled visits will be included in the abnormality or clinically significant/extreme value summaries and in listings only.

All scheduled laboratory data will be summarized in International System units. Conversion for local laboratories will be performed according to the study Local Lab Conventions.

All laboratory data will be listed by part, cohort, participant identification number, and visit/time. If normal ranges are available, abnormalities will be flagged.

For each laboratory test (quantitative and qualitative), the Baseline value is defined as the last non-missing measurement collected/derived prior to the first study treatment administration at C1D1.

For the quantitative laboratory test, the change from Baseline value at each post-baseline visit will be calculated as the difference between the measurement obtained at the specific post-baseline visit, and the Baseline value.

Serum Chemistry parameters will be assessed using the NCI-CTCAE v5.0 grading, as applicable. Hematology parameters will be assessed using the NCI-CTCAE v5.0 grading to assess anemia, leukopenia, neutropenia, febrile neutropenia, lymphopenia, and thrombocytopenia.

Hepatic function abnormality will be assessed by categorizing ALT/AST as $\geq 2x$, $3x$, $5x$, $10x$ upper limit normal (ULN), total bilirubin $\geq 1x$, $1.5x$, $2x$ ULN and alkaline phosphatase $\geq 1x$, $2x$ ULN. To assess potential Hy's law events, the following criteria will be used: an increase in AST and/or ALT to $\geq 3 \times$ ULN concurrent with an increase in total bilirubin to $\geq 2 \times$ ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase $< 2 \times$ ULN).

For the qualitative laboratory parameters (urinalysis, etc.), the presence or absence ('Present' or 'Absent') of each parameter will be recorded as appropriate.

4.5.4 Vital Signs Evaluations

Vital signs evaluations are performed at Screening, at 1 and 2 hours post-dose on Day 1 of Cycle 1, on Days 8, 15, and pre-dose on Day 22 of Cycle 1, pre-dose and at 1 and 2 hours post-dose on Day 1 of Cycle 2, on Day 15 of Cycle 2, pre-dose on Day 1 of Cycles 3-12, and Day 1 of Cycle 13 & every 3 cycles thereafter, as well as EoT and Safety Follow-up Visit in accordance with the SoA (Sections 1.2-1.4 of the protocol).

The following variables were collected:

- Height (cm) (Screening only)



- Weight (kg) (Screening and Day 1 of Cycles 3-12, 13 & every 3 cycles thereafter only)
- Body temperature (°C)
- Pulse oximetry
- Respiratory rate
- Heart rate (bpm)
- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg).

For each vital sign variable, the Baseline value is defined as the last non-missing measurement collected/derived prior to the first study treatment administration at C1D1.

For each variable (except Height), the change from Baseline value at each post-baseline visit will be calculated as the difference between the measurement obtained at the specific post-baseline visit, and the Baseline value.

Potentially clinically important vital sign results will be summarized separately. These criteria are defined as increases in blood pressure and weight changes:

- SBP (≥ 180 mmHg, ≥ 200 mmHg or change from baseline ≥ 30 mmHg).
- DBP (≥ 100 mmHg, ≥ 120 mmHg or change from baseline ≥ 20 mmHg)
- Heart rate (<50 bpm and >100 bpm and change from baseline > 20 bpm)
- Weight increased $\geq 10\%$ from baseline.
- Weight decreased $\geq 10\%$ from baseline.

All vital signs will be listed.

4.5.5 Physical Examination Evaluations

A physical examination will be required at Screening and at Day 1 of Cycles 1-13 and every 3 cycles after that, as well as EoT and Safety Follow-up Visit in accordance with the protocol SoA.

During the Screening Visit and EoT Visit, the physical examination should include 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. It is not planned to capture individual interpretations for each body system for Physical Examinations. Instead, an overall interpretation will be recorded, and if it is considered a clinically significant finding, it will be documented on the Medical History/Adverse Event (MH/AE) form, depending on when it occurred.

The Baseline value is defined as the last non-missing measurement at or prior to the first study treatment administration at C1D1.

At other visits (or as clinically indicated), abbreviated physical examinations with ECOG performance status may be performed (to always include cardiovascular, respiratory, gastrointestinal, and dermatological as well as any other symptom-directed organ system).



4.5.6 Eastern Cooperative Oncology Group (ECOG) Status

ECOG performance status will be assessed as part of the physical examination at Screening and at Day 1 of Cycles 1-13 and every 3 cycles after that, as well as at the EoT Visit and the Safety Follow-up Visit as described in the SoA.

The Baseline value is defined as the last non-missing measurement at or prior to the first study treatment administration at C1D1.

4.5.7 Electrocardiogram (ECG) Evaluations

In Part 1, triplicate 12-Lead electrocardiogram (ECG) evaluations are performed at Screening, C1D1, and C2D1 at the timepoints specified in the SoA (Sections 1.2-1.4 of the protocol). Single 12-Lead ECG evaluations are performed at Day 1 of Cycles 3, 5, 7, 9, 11, 13, and every 3 cycles thereafter, as well as the End of Treatment (EoT) Visit and the Safety Follow-up Visit at the timepoints specified in the SoA. At C1D1, C2D1, C3D1, C5D1, C7D1, C9D1, C11D1, C13D1, and Day 1 of every 3 cycles thereafter, as well as at EoT Visit and the Safety Follow-up Visit, an overall safety ECG assessment will be completed by the investigator.

In Part 2, triplicate 12-Lead ECG evaluations are performed at Screening, C1D1, and C2D1 at the timepoints specified in the SoA. Single 12-Lead ECG evaluations are performed at Day 1 of Cycles 4, 6, 8, 10, 12, 13, and every 3 cycles thereafter, as well as the End of Treatment (EoT) Visit and the Safety Follow-up Visit at the timepoints specified in the SoA. At C1D1, C2D1, C3D1, C5D1, C7D1, C9D1, C11D1, C13D1, and Day 1 of every 3 cycles thereafter, as well as at EoT Visit and the Safety Follow-up Visit, an overall safety ECG assessment will be completed by the investigator.

Triplicate ECG assessments are to be performed in succession, approximately 3 minutes apart, and the triplicate recordings will be averages to give the results for a given visit and parameter.

Table 9 presents the quantitative and qualitative ECG parameters that will be collected. Investigator's overall assessment of ECG will also be assessed and recorded at the timepoints specified in the SoA and will be classified as Normal, Abnormal Clinically Insignificant, or Abnormal Clinically Significant.

Table 9 ECG Parameters

ECG Parameters (Unit)
Conduction Times
HR (bpm)
PR interval (msec)
RR interval (msec)
QRS interval (msec)
QT interval (msec)
QTcF interval (msec)

Abbreviations: HR= heart rate; PR= pulse rate; RR= R-R interval; QRS= QRS complex; QT = QT interval; QTcF= QT corrected by Fridericia's cube root



The baseline value for a given participant and parameter is the last measurement taken before dosing began (pre-dose on Day 1 of Cycle 1).

A summary of ECG parameters including heart rate (beats/min), QT interval (msec), RR interval (msec), QRS (msec), QTcF (msec), and change from baseline (for only QTcF) will be presented for each planned visit. When a triplicate ECG is obtained, the average of the 3 values should be calculated for each parameter.

Per ICH E14 category, the following categories will be applied for average QTcF: Value >480 and ≤ 500 msec; >500 msec; Change from Baseline as increase ≤ 30 msec, >30 to ≤ 60 msec, and by >60 msec. A shift from baseline to worst CTCAE grade summary of averaged QTcF will also be presented.

QTcF will be graded per CTCAE v5.0. the grades are as follows:

- Grade 1: value 450 to 480 msec
- Grade 2: value >480 to 500 msec
- Grade 3: value >500 or change from baseline >60 msec
- Grade 4: Torsade de Pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia. Grade 4 events will be reviewed by the study Medical Monitor from clinical data. As it is based on clinical judgment and not based on QTcF numerical results, Grade 4 QTcF will not be presented in the summary table.

4.5.8 Ophthalmological Examinations

Ophthalmological examinations will be conducted at Screening and at Day 1 of Cycle 3 and every 2 cycles thereafter until Cycle 13, and then Day 1 of every 3 cycles thereafter, as well as the End of Treatment Visit as described in the SoA. The examination will include the visual acuity, intraocular pressure (provided as a numerical value), slit lamp examination, cup-to-disc ratio, and optical coherence tomography (OCT), as well as Investigator's Overall Assessment. Other methods may be performed if indicated by the investigator, an optometrist, or the ophthalmologist (e.g., dilated funduscopy, fluorescein angiography, etc.).

The Baseline value is defined as the last non-missing measurement at or prior to the first study treatment administration at C1D1.

4.5.9 Left Ventricular Ejection Fraction (LVEF) Assessment

LVEF will be assessed at Screening, at Day 1 of Cycle 3, and every 2 cycles thereafter until Cycle 13, and then Day 1 of every 3 cycles thereafter, as well as at the End of Treatment Visit as described in the protocol SoA. LVEF can be assessed by ECHO or MUGA. The same imaging technique should be used in a participant throughout the study. In addition to the results from ECHO or MUGA, participants will be evaluated for any clinical symptoms of cardiac failure (such as shortness of breath, exercise intolerance, and peripheral edema).

The Investigator will give their overall assessment of LVEF as normal or abnormal, and if abnormal, if clinically significant or not.

The Baseline value is defined as the last non-missing measurement at or prior to the first study treatment administration at C1D1.

4.6 Other Measures

4.6.1 Participant Disposition

Participant disposition data is collected on the 'End of Study Participation' case report form (CRF) page when a participant stops study treatment. The following data will be summarized:

- Participants who receive at least one dose of mirdametinib
- Participants who receive at least one dose of brimrafenib
- Participants who complete Cycle 1
- Length of study participation in number of cycles
- Participants who are ongoing to be treated
- Participants who have prematurely discontinued/withdrawn from treatment
- Primary reason for discontinuing the treatment period
- Reason for discontinuation from study
- Reason for withdrawal of consent
- Participants participating in the long-term follow-up

The analysis sets defined in Section 3 will be analyzed and presented as part of the participant disposition data.

4.6.2 Protocol Deviations

Protocol deviations are reviewed in accordance with the Protocol Deviation Plan. All deviations will be reviewed prior to database lock to determine which deviations are deemed important to report in the CSR in accordance with ICH E3 guidelines. Important protocol deviations are defined as those potentially impacting safety or efficacy assessments and analyses. Additional details regarding which deviations should be considered important can be found in the Protocol Deviation Plan provided by the medical team.

- Important protocol deviations for all enrolled participants will be summarized by category, by cohort in Part 1 and the cohorts in Part 2 important protocol deviations will be listed.

4.6.3 Demographics

Demographic data is collected on the 'Demographics' CRF page at Screening. The following data will be summarized:

- Age at time of consent
- Sex at Birth
- Childbearing potential at Screening
 - If no, specify reason
- Ethnicity
- Race

Missing demography data will be handled according to the rules specified in Section 4.10.3.

4.6.3.1 Baseline Participant Characteristics

Baseline participant characteristics include characteristics that participants presented with prior to the first administration of study treatment. The last available vital signs variables, laboratory results and ECG parameters collected prior to the first administration of study treatment will be presented as collected per protocol.

4.6.3.2 Baseline Disease Characteristics

Tumor history and location is recorded at Screening on the 'Cancer History' CRF page. History of prior cancer surgeries, radiotherapies and systematic anti-cancer therapies are collected on the 'Prior Surgery', the 'Prior Radiotherapy', and the 'Prior Systemic Therapy' CRF pages.

The full list of disease characteristics in summaries may include:

- Type of cancer diagnosis and mutation
- Time since initial diagnosis
- Time since first metastatic disease
- History of prior cancer surgery
- History of prior radiotherapy
- History of prior systemic anti-cancer therapy
- Number of prior lines of therapy

4.6.4 Medical History

Medical history contains information about conditions that a participant might have suffered from prior to the first administration of study treatment at C1D1, or conditions that are ongoing at the time of the first administration of study treatment.

Medical history includes any history of clinically significant disease or surgery.

Medical history will be summarized by cohort.

4.6.4.1 Coding of Medical History Terms

The medical history term (Investigator term) is assigned to the LLT, and a PT will be classified by a HLT, a HLGT and a SOC according to the MedDRA thesaurus, Version 27.1 or higher, depending on the latest version available during the study.

Although there can be multiple SOC for a PT, each PT will be linked with one SOC, namely the primary SOC which is automatically assigned by MedDRA via one HLT, HLGT route.

The following coding data will be presented:

- LLT
- PT
- Coding data per primary SOC
 - HLT
 - HLGT

Medical history will be reported on a per-participant basis. This means that even if a participant suffered the same clinical event repeatedly (i.e., events mapped to the same PT), the event will be counted only once, and the earliest date will be regarded as the start date of the event and the latest date will be regarded as the stop date of the event.

The same rule for counting applies for PTs mapped to the same HLT and for HLTs mapped to the same HLGT and for HLGTs mapped to the same SOC.

4.6.5 Concomitant and Prior Medications and Procedures

Concomitant medications are defined as any medication (i.e., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) taken at any stage from the time of informed consent until 30 days after the last dose of study treatment. Medications will be considered prior if they were used by the participant within 28 days of and stopped before the first dose of study treatment on Cycle 1 Day 1.

Concomitant and prior medications data are collected throughout the study on the 'Concomitant Medications' CRF page.

Missing concomitant and prior medications data will be handled according to the rules specified in Section 4.10.1.

4.6.5.1 Coding of Concomitant Medication Terms

Concomitant medications are classified according to active drug substance using the World Health Organization-Drug Dictionary (WHO-DD), Version September 2024 or higher, depending on the latest version available during the study.

The WHO-DD drug identity (ID) has 11 characters. The preferred name, for example, the salt/ester of the substance is defined by the first 8 characters, and the WHO-DD name is defined by the 11 characters.

In this study, anatomical therapeutic chemical (ATC) codes are defined to the 4th level. Although there can be multiple ATC classes for a drug, each drug will be linked with one ATC class which will be assigned manually during the coding process, based on information about the indication and route in relation to the study therapeutic area. This one ATC class will be indicated as the 'primary' ATC class, and only the primary class will be presented.

4.7 General Statistical Methods

4.7.1 General Information

All analysis datasets and outputs will be produced by the Biometrics Department of SpringWorks/MapKure using the SAS® system Version 9.4 or higher.

4.7.2 Default Descriptive Statistics and Data Rules

Unless otherwise stated, summary statistics including the number of participants, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum, will be presented for all continuous variables. Minimum and maximum values will be presented to the same decimal precision as the raw values, the mean, median, and quartile values to one more, and the standard deviation, to two more decimal places than the raw values. These will be presented by cohort.

For categorical variables, per category, the absolute counts (n) and percentages (%) of participants with data, and if appropriate, the number of participants with missing data, will be presented. These will be presented by cohort. All percentages will be presented to one decimal place, except for 100% which will be presented as '100%' and less than 0.1% which will be presented as '<0.1%'. In the case of a 0 count the percentage will not be presented.

For adverse events reported on a per-participant basis, medical history and concomitant medications and procedures, the denominator for the percentage calculation will be the number of participants in each cohort.

4.8 Hypotheses and Decision Rules

4.8.1 Primary Hypothesis

No formal primary hypothesis will be tested.

4.9 Covariates

No covariates will be used in the analysis of study endpoints.

4.10 Handling of Missing Data

Missing data will only be imputed in the following cases:

4.10.1 Adverse Events and Prior/Concomitant Medication

Missing and/or incomplete dates for AEs or prior/concomitant medications are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the AE or medication is "Ongoing".

The imputed missing dates will be used for programming derivation such as TEAEs, the actual non-imputed dates will be used on all the related listings. The following rules will be followed. (Note that the study treatment means BGB-3245 and /or mirdametinib in this SAP.)

Start date

- If the start date is completely missing (i.e., the day, month, and year are all unknown), the start date will be set to the date of the study treatment administration date.

Missing day only



- If the month and year of the incomplete date are the same as the month and year of the study treatment administration date, then the day of the study treatment administration date will be assigned to the missing day.
- If either the year is before the year of the study treatment administration date or if years are the same, but the month is before the month of the study treatment administration date, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the study treatment administration date or if both years are the same, but the month is after the month of the study treatment administration date, then the first day of the month will be assigned to the missing day.

Missing month only

- The day will be treated as also missing and both month and day will be replaced according to the procedure below.

Missing day and month

- If the year of the incomplete date is the same as the year of the study treatment administration date, then the day and month of the study treatment administration date will be assigned to the missing fields.
- If the year of the incomplete date is not the same as the year of the study treatment administration date, then January 1 will be assigned to the missing fields.

If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Stop date

Missing day only

- If the month and year of the incomplete date are the same as the month and year of the last visit date, then the day of the last visit date will be assigned to the missing day.
- If either the year is before the year of the last visit date or if both years are the same, but the month is before the month of the last visit date, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last visit date or if both years are the same, but the month is after the month of the last visit date, then the first day of the month will be assigned to the missing day.

Missing month only

- The day will be treated as missing, and both month and day will be replaced according to the procedure below.

Missing day and month



- If the year of the incomplete date is the same as the year of the last visit date, then the day and month of the last visit date will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the last visit date, then 31st December will be assigned to the missing fields.

If the year of the incomplete date is after the year of the last visit date, then 1st January will be assigned to the missing fields.

The imputation method will only be used to determine the time of the event relative to the first administration of study treatment.

In the occasion of missing severity data for an AE, no imputation will be performed, and severity will be presented as “Missing” in summary tables.

If no coding information is available for a specific AE, the AE will be presented as an ‘Uncodable Event’ in summary tables.

4.10.2 Death

Incomplete dates of death will be imputed as follows:

If only ‘day’ is missing, then impute with the first day of the month. If ‘day’ and ‘month’ are missing and ‘year’ is not missing and is the same as the year of the last contact date, then impute as the date of the last contact +1 day.

If ‘day’ and ‘month’ are missing and ‘year’ is not missing and is greater than the year of the last contact date, then impute as 1st January of that year. If the imputed death date is less than the last contact date, then set to the last contact date + 1 day. This imputation will only be applied for the calculation of OS, otherwise the data will be presented as missing in listings.

4.10.3 Demographics

For determining age when the date of birth is not known completely, a missing day only will be imputed as the 15th, a missing day and month will be imputed as the 2nd of July which is day 183 in the year.

4.10.4 Windowing Conventions

Table 10 presents the visit windows that will be used to assign assessments to a nominal visit.

Table 10 Visit Windows

Visit	Visit Label	Visit Day	Visit Window
Screening	Screening	-28	Day -28 to -1
Cycle 1 – Week 1 (Baseline, study visit day 1)	C1D1	1	Day 1
Cycle 1 – Week 2 (Cycle Day 8 ±1)	C1D8	8	±1 days



Visit	Visit Label	Visit Day	Visit Window
Cycle 1 – Week 3 (Cycle Day 15 ±2)	C1D15	15	±2 days
Cycle 1 – Week 4 (Cycle Day 22 ±2)	C1D22	22	±2 days
Cycle 2 – Week 5 (Cycle Day 1 +2)	C2D1	29	+2 days
Cycle 2 – Week 7 (Cycle Day 15 ±2)	C2D15	43	±2 days
Cycle 3 – Week 9 (Cycle Day 1 ±2)	C3D1	57	±2 days
Cycle 4 – Week 13 (Cycle Day 1 ±2)	C4D1	85	±2 days
Cycle 5 – Week 17 (Cycle Day 1 ±2)	C5D1	113	±2 days
Cycle 6 – Week 21 (Cycle Day 1 ±2)	C6D1	141	±2 days
Cycle 7 – Week 25 (Cycle Day 1 ±2)	C7D1	169	±2 days
Cycle 8 – Week 29 (Cycle Day 1 ±2)	C8D1	197	±2 days
Cycle 9 – Week 33 (Cycle Day 1 ±2)	C9D1	225	±2 days
Cycle 10 – Week 37 (Cycle Day 1 ±2)	C10D1	253	±2 days
Cycle 11 – Week 41 (Cycle Day 1 ±2)	C11D1	281	±2 days
Cycle 12 – Week 45 (Cycle Day 1 ±2)	C12D1	309	±2 days
Cycle 13 – Week 49 (Cycle Day 1 ±3)	C13D1	337	±3 days
Cycle XX – Week 4*(XX-1)+1 (Cycle Day 1 ±3)	CXXD1	28*(XX-1)+1	±3 days
Safety Follow-up – 30 ±7 days after last dose	Safety Follow-up		±7 days
Long-term Follow-up – Every 3 months ±7 days after last dose	Long-term Follow-up		±7 days

Unscheduled visits will be mapped to the nearest planned visit by study visit day.

The Study Visit Day of an event/assessment will be calculated relative to the first study treatment administration at C1D1. The Study Visit Day of events/assessments occurring before the first administration will be calculated as follows:

Study Visit Day = (Date of assessment/event - Date of first study treatment administration at C1D1).

For events/assessments occurring at Baseline or post-baseline, Study Day will be calculated as follows:

Study Visit Day = (Date of assessment/event - Date of first study treatment administration at C1D1) + 1.

4.11 Interim Analyses

For Part 2 of the study there will be an interim analysis in each Cohort A, B, and C once approximately 50% of the planned total sample size is evaluable for ORR (approximately 10 evaluable participants in Cohort A and 15 evaluable participants in Cohorts B and C). The goal of the IA will be to determine if the anti-tumor efficacy and tolerability of study treatments administered at the RP2D meets the Sponsor's predefined criteria for the clinical proof-of-concept (PoC).



The interim analysis will consist of all available safety, efficacy, PK and PDx data and the stopping criteria following the BOP2 design will be assessed. Stopping criteria for each cohort.

Based on the results of any of the interim analyses, the study/cohort may be continued, modified, or stopped by the Sponsor. The expansion cohorts may be expanded if deemed appropriate by the Sponsor based on the analysis of all available safety, efficacy, PK, and PDx data from that cohort and the consultation with the Regulatory Authorities (if applicable).

5 STATISTICAL ANALYSES

5.1 Participant Disposition

Participant disposition information, as listed in Section 4.6.1, will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of participants with data in the relevant cohort. This summary will be presented for the safety population.

5.2 Protocol Deviations

Protocol Deviations will be summarized by severity (important/minor) by absolute counts (n) and percentages (%). Percentages will be based on the number of participants with data. This summary will be presented for the safety population.

5.3 Demographics

Baseline demographics data as laid out in Section 4.6.3 includes continuous and categorical variables. Continuous variables will be summarized by the number of participants, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum values. Categorical variables will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of participants with data in the relevant cohort. These summaries will be presented for the Safety Population.

5.3.1 Baseline Participant Characteristics

Baseline participant characteristics, as listed in Section 4.6.3.1, include continuous and categorical variables. Continuous variables will be summarized by the number of participants, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum values. Categorical variables will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of participants with data. These summaries will be presented for the Safety Population. Baseline participant characteristics analysis will not be completed.

5.3.2 Baseline Disease Characteristics

Baseline disease characteristics, as listed in Section 4.6.3.2, include continuous and categorical variables. Continuous variables will be summarized by the number of participants, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum values. Categorical variables will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of participants with data in the relevant cohort. These summaries will be presented for the Safety Population.



Additional summaries will be presented by absolute counts (n) and percentages (%) of participants who have prior cancer surgery, prior radiotherapy or prior systemic anti-cancer therapy for the Safety Population.

Prior cancer surgery will be presented by SOC and preferred term as laid out in Section 4.6.4.1. Number of participants with at least one prior systemic anti-cancer therapy recorded, 4th level ATC codes and preferred terms will be summarized by absolute counts (n) and percentages (%) for the Safety Population. Percentages will be calculated based on the number of participants in the Safety Population.

5.4 Medical History

Medical history will be summarized by absolute counts (n) and percentages (%) for the Safety Population. All medical history records will be presented by SOC and preferred term as laid out in Section 4.6.4.1. Percentages will be calculated based on the number of participants in each cohort.

All medical history data will be listed.

5.4.1 Concomitant and Prior Medication

Number of participants with at least one recorded concomitant medication, 4th level ATC codes and preferred terms will be summarized by absolute counts (n) and percentages (%) for the Safety Population. Percentages will be calculated based on the number of participants in each cohort.

All prior and concomitant medication data will be listed.

5.4.2 Concomitant and Prior Procedures

All prior and concomitant procedures data will be listed. Concomitant and prior procedures analysis will not be completed due to the early termination of the study.

5.5 Study Drug Exposure

Study drug exposure definitions are outlined in Table 11 below.

Table 11 Study Drug Exposure Definitions

Variable	Definition
Study treatment duration (months)	The minimum of: (the death date – the first dose date + 1)/30.4375 (analysis cutoff date – date of first dose + 1)/30.4375 (the last dose date – the first dose date + 1)/30.4375
Cycle started	A participant is considered to have started a cycle if they received at least one dose of study treatment in that cycle.



Daily dose	Average and median daily dose of mirdametinib and brimrafenib separately based on actual dose participants received during the treatment period including dose interruptions and dose reductions. Average Daily Dose = (Total cumulative dose) / (Duration of exposure in days).
Cumulative amount dispensed (mg)	Sum of the all the available 'Amount Dispensed' collected on the CRF page 'Drug accountability – brimrafenib for each participant.
Cumulative amount returned	Sum of the all the available 'Amount Returned' collected on the CRF page 'Drug accountability – brimrafenib for each participant.
Dose interruptions	Number of days relative to the study treatment duration the dose was interrupted.
Dose reductions	Number of days relative to the study treatment duration the dose was reduced.
Relative dose intensity	Actual cumulative dose of each mirdametinib and brimrafenib separately, relative to the planned dose over the full treatment period in days expressed in percentages.
Treatment Compliance (%)	Total cumulative dose received in mg during the whole study period) / (Expected number of days x initial assigned dose level at enrollment in mg).
Total Cumulative Dose	Total amount of dose (mg) over time.

Descriptive statistics will be provided for the total cumulative dose (mg), duration of exposure (months), relative dose intensity, and average daily dose.

The treatment compliance rate will be categorized as >120%, >100-120%, 80-100%, or <80%. Treatment compliance will be summarized for mirdametinib and brimrafenib compliance separately. This summary will be created for the Safety Population by cohort.

5.6 Primary Objective Analyses

The study endpoints will include collected and derived continuous and categorical variables. Continuous variables will be summarized by the number of participants, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum values. Categorical variables will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of participants with data.

The Safety Population will be the primary analysis set of interest for safety analyses. The Efficacy Evaluable Population will be the primary analysis set of interest for efficacy analyses. The DLT Evaluable Population will be used to describe DLTs.



5.6.1 Part 1 and 2: Evaluate the safety and tolerability of mirdametinib and brimarafenib administered as a combination in the eligible participant population.

The analysis set for this objective is the Safety Population.

5.6.1.1 Adverse Events

Only TEAEs will be presented in summary tables as defined in Section 4.5.2.1. An overview of all AEs will be presented by cohort and overall AEs. Separate summaries by SOC and PT will be provided for incidence of AEs, incidence of AEs by cycle of first onset, incidence of AEs by highest severity, incidence of SAEs, AEs of at least Grade 3 severity, AEs related to mirdametinib, AEs related to brimarafenib, AEs related to mirdametinib by highest severity, AEs related to brimarafenib by highest severity, AEs related to study procedures, AEs leading to discontinuation or dose modification including dose interruption or reduction, and mirdametinib and brimarafenib AESIs – all as defined in Section 4.5.2.1. A summary of AEs by PT only will also be provided. All summaries will present absolute counts (n) and percentages (%) calculated based on the number of participants in each cohort.

AEs by cycle of onset will also be summarized and present absolute counts (n) and percentages (%) calculated based on the number of participants in the Safety Population that entered the cycle. A separate summary by SOC and PT will be provided for incidence of AEs including participant counts and event counts.

5.6.1.2 Clinical Laboratory Parameters

All clinical laboratory parameters listed in Section 4.5.3 except for urinalysis will be grouped by category and summarized by visit and by cohort. Absolute values and, where applicable, change from baseline for quantitative parameters will be summarized by box and whisker plots for hematology and chemistry. In addition, hepatic function will be summarized by Hy's law plot.

Shift tables based on the NCI-CTCAE v5.0 toxicity grading will be presented for each laboratory parameter (except urinalysis) between baseline and each post-baseline visit.

5.6.1.3 Vital Signs Evaluations

Absolute value and change from baseline for all vital signs parameters as listed in Section 4.5.4 will be summarized by visit. Continuous variables will be summarized by the number of participants, mean, standard deviation, median, lower quartile, upper quartile, and minimum and maximum values.

5.6.1.4 Physical Examination Findings

Any physical examination findings will be listed. The number of participants with a physical examination finding will be summarized by absolute counts (n) and percentages (%) by visit. Percentages will be based on the number of participants with data in each relevant cohort.

5.6.1.5 Eastern Cooperative Oncology Group (ECOG) Status

ECOG status will be summarized by absolute counts (n) and percentages (%) by visit using the definitions given in Table 12. Percentages will be based on the number of participants with data in each relevant cohort.

A shift table for status score will also be presented between baseline and each post-baseline visit.

Table 12 ECOG Performance Status definitions

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

5.6.1.6 Electrocardiogram (ECG) Evaluations

Absolute value and change from baseline for all ECG parameters as listed in Section 4.5.7 will be summarized by visit as per Section 4.7.2. Additionally, summaries will be provided by post-baseline visit for the following categories:

- Number (%) of participants with QTcF between 450 and 480.
- Number (%) of participants with QTcF between 480 and 500.
- Number (%) of participants with QTcF >500.
- Number (%) of participants with QTcF change from baseline ≤ 30 .
- Number (%) of participants with QTcF change from baseline >30 and ≤ 60 .
- Number (%) of participants with QTcF change from baseline >60.

These summaries will be presented as per Section 4.5.7.

5.6.1.7 Ophthalmological Examinations

The Investigator's overall assessment of the ophthalmological examination ('Normal', 'Abnormal, Clinically Insignificant', 'Abnormal, Clinically Significant') for each eye will be summarized by absolute counts (n) and percentages (%) by visit. Percentages will be based on the number of participants with data.

Absolute value and change from baseline for intraocular pressure will be summarized by visit as a continuous parameter by the number of participants, mean, standard deviation, median, lower quartile, upper quartile, and minimum and maximum values.

NCI-CTCAE v5.0 Vision decreased grades will also be summarized at each post-baseline visit by absolute counts (n) and percentages (%) using the definitions given in and with reference to



Appendix (see Table 13). For Grade 2 and 3, a baseline recording of visual acuity is required. Percentages will be based on the number of participants with data. Ophthalmologic examination analysis will not be completed.

Table 13 NCI-CTCAE v5.0 Vision decreased grading

Grade	Description
1	NA*
2	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)
3	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)
4	Best corrected visual acuity of 20/200 or worse in the affected eye
5	NA*

*not applicable (NA) according to NCI-CTCAE v5.0

5.6.1.8 Left Ventricular Ejection Fraction (LVEF) Assessment

The LVEF result will be summarized by visit as a continuous parameter by the number of participants, mean, standard deviation, median, lower quartile, upper quartile, and minimum and maximum values. The Investigator's overall interpretation of LVEF ('Normal', 'Abnormal, Clinically Insignificant', 'Abnormal, Clinically Significant') will be summarized by absolute counts (n) and percentages (%) by visit. Percentages will be based on the number of participants with data.

5.6.2 Part 1 only: Determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for mirdametinib and brimarafenib administered as a combination in the eligible participant population.

The MTD is determined using the dose escalation plan based on the BOIN design. The target toxicity rate used for the MTD identification is $\phi=0.3$. The dose escalation plan is described in full in Section 2.3.1. The number of DLTs will be summarized by the absolute counts (n) and percentages (%) of participants with data in each dosing cohort of the DLT Evaluable Population. DLTs are defined in Section 6.4 of the Protocol.

The RP2D will be determined by the CMC, considering the MTD as calculated by the isotonic regression analysis based on the observed DLTs in the dose escalation cohorts for the DLT evaluable population and other safety data described in Section 5.6.1.

The analysis set for this objective is the DLT Evaluable Population.

5.6.3 Part 2 only: Determine the preliminary anti-tumor efficacy for the RP2D of mirdametinib and brimarafenib administered as a combination in the eligible participant population.

Anti-tumor efficacy will be measured by the Objective Response Rate (ORR) defined as the portion of participants with a confirmed response (complete response (CR) + partial response



(PR)), using RECIST v1.1. A confirmed response is defined as in Section 4.1.3. This analysis will not be performed because of the early termination of the study.

RECIST v1.1 response status will be summarized for Part 2 by visit and by cohort as per Section 4.1.3. Additionally, the best overall response rate for each cohort at time of final analysis will be reported with 95% CI using Clopper-Pearson method.

Measurement of LD and percentage change from baseline in LD will be summarized by visit. The analysis set for this objective is the Efficacy Evaluable Population.

The results of the antitumor efficacy of mirdametinib and brimarafenib will be presented in summary tables and figures, specifically in waterfall and swimmer plots to illustrate the results for each of the cohorts in Part 2.

5.7 Secondary Objective Analyses

5.7.1 Part 1 only: Determine the preliminary anti-tumor efficacy of mirdametinib and brimarafenib administered as a combination in the eligible participant population.

Anti-tumor efficacy will be measured by the Objective Response Rate (ORR) defined as the portion of participants with a confirmed response (complete response (CR) + partial response (PR)), using RECIST v1.1. A confirmed response is defined as in Section 4.1.3.

RECIST v1.1 response status will be summarized for Part 1 by visit and by dosing cohort. Section 4.6.2. Additionally, the best overall response rate at time of final analysis will be reported with 95% CI using Clopper-Pearson method.

The analysis set for this objective is the Efficacy Evaluable Population.

5.7.2 Part 1 and Part 2: Determine duration of response in participants treated with the combination of mirdametinib and brimarafenib.

Median DOR and associated 95% CIs will be presented overall and by cohort. Kaplan-Meier plots of DOR will be presented separately for the overall population and by cohort. Derivation of duration of response will use all available data at the time of analysis.

The analysis set for this objective is the Efficacy Evaluable Population. DOR will only be done if there are responses.

5.7.3 Determine the PK of mirdametinib and brimarafenib administered as a combination in the eligible participant population (Part 1 and Part 2).

Because of the early termination as stated in the introduction section, no formal PK analysis is planned, a listing of measured concentrations will be presented.

5.8 Exploratory Objective Analyses

5.8.1 Part 2 only: Determine if the combination of mirdametinib and brimarafenib delays disease progression in this participant population

Median TTP, with associated 95% CIs will be presented for each cohort in Part 2. Kaplan-Meier plots of time-to-progression for all participants in Part 2 and for each cohort in Part 2 will be produced separately .

Median PFS, with associated 95% CIs will be presented for each cohort in Part 2. Kaplan-Meier plots of progression-free survival for all participants in Part 2 and for each cohort in Part 2 will be produced separately. Median TTP and PFS will not be analyzed because of the early termination.

The analysis set for this objective is the Efficacy Evaluable Population.

5.9 Other Safety Analyses

5.9.1 Exposure to Study Treatment

Exposure to Study Treatment includes derived continuous and categorical variables specified in Section 4.5.1. Continuous variables will be summarized by the number of participants, mean, standard deviation, median, lower quartile, upper quartile, and minimum and maximum values. Categorical variables will be summarized by absolute counts (n) and percentages (%). Percentages will be based on the number of participants with data.

6 CHANGES TO THE PLANNED ANALYSES

Clarification that analyses (ORR and DOR) require responses that are confirmed.

Due to the early termination of the study and limited data Part 2 analysis including interim analysis was not completed. Changes for Part 1 analysis included limiting efficacy analysis to objective response and removed the following safety analysis urinalysis, baseline participant characteristics, ophthalmologic assessments and concomitant and prior procedures. Formatting issues were revised.

Additionally, PK analysis was not done due to the limited samples collected.

7 REFERENCES

Liu, S, and Y Yuan. 2015. "Bayesian Optimal Interval Designs for Phase I Clinical Trials." J R Stat Soc Ser C Appl Stat 64: 507–23.

Zhou, H., J. J. Lee, and Y Yuan. 2017. "BOP2: Bayesian Optimal Design for Phase II Clinical Trials with Simple and Complex Endpoints." Statistics in Medicine 36 (21): 3302–14. <https://doi.org/10.1002/sim.7338>.



8 ATTACHMENTS AND APPENDICES

8.1 Appendix 1 RECIST Criteria v1.1

8.1.1 Response Criteria: Evaluation of target lesions

Response Category	Definition
Complete Response (CR)	Disappearance of all target lesions.
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum of LD recorded since the treatment started or the appearance of one or more unequivocal new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

8.1.2 Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the start of study treatment). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria (defined below).

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=Complete Response; NE=Not Evaluable; PD=Progressive Disease; PR=Partial Response; SD=Stable Disease.



Participants with a global deterioration of health status requiring discontinuation of study treatment without objective evidence of disease progression at that time will be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

The following table presents the result of a confirmed response based on subsequent assessments*

First Time Point Response**	Second Time Point Response	Confirmed Response (Best Overall Response)*
CR	CR	CR
CR	PD	SD or PD (1)
CR	NE (4) **	SD or NE (2)
PR	CR	PR
PR	PR	PR
PR	SD (3)**	SD
PR	PD	SD or PD (1)
PR	NE (4) **	SD or NE (2)
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	PD	SD or PD (1)
SD	NE	SD or NE (2)
PD	No further evaluation	PD
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	PD	PD
NE	NE	NE

Abbreviations: CR=Complete Response; PR=Partial Response; SD=Stable Disease; PD=Progressive Disease; NE= Not Evaluable.

- * A Best Overall Response of SD can only be made after the participant is on-study for minimum 12 weeks. If the participant is on-study less than 12 weeks, any tumor



assessment indicating stable disease before this time period will have a Best Overall Response of NE unless PD is identified.

- ** Subsequent documentation of CR may provide confirmation of a previously identified CR for participants where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for participants where the second integrated response was NE or SD. If the third Time Point Response (TPR) confirms the CR (or PR) then the Confirmed Response will be CR (or PR). For this study, only one (1) intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, one (1) SD is allowed between PRs (e.g., PR SD PR = PR)
- (1) Best Overall Response will be SD if the first TPR is minimum 12 weeks on-treatment. Otherwise, the best overall response will be PD.
 - (2) Best Overall Response will be SD if the first TPR is minimum 12 weeks on-study. Otherwise, the best overall response will be NE.
 - (3) TPR is SD if the increase from the first to the second assessment does not qualify for PD.
 - (4) For participants with unconfirmed CR/PR and who subsequently drop off the study, the best overall response will be SD.



8.2 Appendix 2

8.2.1 List of Tables, Listings and Figures

The List of Tables, Listings and Figures will be supplied as a separate document as an attachment to this Statistical Analysis Plan.



8.2.2 Plan Version History

Version	Effective Date	Changes	Author / Modified By
1.0	28 June 2024	Initial Version	Martin Roessner
1.1	31 July 2024	Administrative Change to correct formatting issue in the footers. Updated author information.	Vincent Amoruccio
2.0	6 November 2024	<p>The study is terminated early, shifting the statistical analysis plan to focus primarily on safety. No interim analysis will be conducted because of the early termination.</p> <p>Some efficacies analyses will not be completed because of the early termination.</p> <p>All Part 2 related sections will not be completed due to the early termination of the study.</p>	Getie Zewdie



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