Protocol

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This trial protocol has been provided by the authors to give readers additional information about the work.

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PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF DIVARASIB VERSUS SOTORASIB OR ADAGRASIB IN PATIENTS WITH PREVIOUSLY TREATED *KRAS G12C*-POSITIVE ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BO45217
VERSION NUMBER:	1
TEST PRODUCT:	Divarasib (RO7435846)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIERS:	IND Number: 147339 EU CT Number: 2024-510908-37-00 PS ID: To be determined CIV ID: To be determined NCT Number: To be determined
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF DIVARASIB VERSUS SOTORASIB OR ADAGRASIB IN PATIENTS WITH PREVIOUSLY TREATED *KRAS* G12C-POSITIVE ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BO45217
VERSION NUMBER:	1
TEST PRODUCT:	Divarasib (RO7435846)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor to the contact provided below.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF DIVARASIB VERSUS SOTORASIB OR ADAGRASIB IN PATIENTS WITH PREVIOUSLY TREATED *KRAS G12C*-POSITIVE ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIERS:	IND Number: 147339 EU CT Number: 2024-510908-37-00 PS ID: To be determined| CIV ID: To be determined| NCT Number: To be determined

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of divarasib, a Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine (KRAS G12C) inhibitor, compared to locally approved KRAS G12C inhibitors (sotorasib or adagrasib) in patients with *KRAS G12C*-positive (KRAS G12C+) advanced or metastatic non-small cell lung cancer (NSCLC) who have been previously treated with standard of care treatments in the advanced or metastatic setting. Recently, several KRAS G12C inhibitors have been developed and studied in this patient population; however, the available data to date indicate that an unmet medical need still exists, and that more efficacious KRAS G12C inhibitors with acceptable safety profile and tolerability could improve the long-term outcome for patients.

OBJECTIVES AND ENDPOINTS

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 3.

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: Individuals with KRAS G12C+ advanced or metastatic NSCLC who have received at least one prior systemic therapy • Endpoint: PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) • Treatment: – Experimental arm: divarasib 400 mg QD – Control arm: KRAS G12C inhibitor (sotorasib 960 mg QD or adagrasib 600 mg BID), depending on investigator's choice, as applicable • Intercurrent events and handling strategies: – Early discontinuation from study treatment: treatment policy strategy – Start of non-protocol specified anticancer therapy prior to disease progression: treatment policy strategy • Population-level summary: hazard ratio for PFS

Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: As defined above for PFS • Endpoint: OS, defined as the time from randomization to death from any cause • Treatment: As defined above for PFS • Intercurrent events and handling strategies: – Early discontinuation from study treatment: treatment policy strategy – Start of non-protocol specified anticancer therapy: treatment policy strategy • Population-level summary: hazard ratio for OS
• To evaluate, from the participant's perspective, the functioning and impact of key disease-related symptoms of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: As defined above for PFS • Endpoint: TTCD on the EORTC QLQ-C30 dyspnea item and the physical functioning scale, and the cough scale of the QLQ-LC13 scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration (decrease from baseline in the functioning scale of at least 10 points or increase in the symptom scales of at least 10 points) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death. • Treatment: As defined above for PFS • Intercurrent events and handling strategies: – Early discontinuation from study treatment prior to a confirmed clinically meaningful deterioration: treatment policy strategy – Start of non-protocol specified anticancer therapy prior to a confirmed clinically meaningful deterioration: hypothetical strategy – Death that occurs before participants report any clinically meaningful deterioration: while-alive strategy • Population-level summary: hazard ratio for TTCD
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• ORR, defined as the proportion of participants with a CR or PR, as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first)

• To evaluate the safety and tolerability of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 grading scale • Change from baseline in selected vital signs and ECG parameters • Change from baseline in selected clinical laboratory test results • Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne) as assessed through use of the NCI PRO-CTCAE • Change from baseline in diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne as assessed through use of the NCI PRO-CTCAE • Frequency of participants' response of the degree they are troubled with treatment symptoms, as assessed through use of the single-item EORTC Item List (IL46)
• To evaluate the quality of life of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Change from baseline in cough, chest pain, dyspnea, physical and role functioning, and GHS/QoL at each timepoint as assessed through use of the EORTC QLQ-LC13 and QLQ-C30 • TTCD on the EORTC QLQ-C30 role functioning and GHS/QoL scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration (decrease from baseline of at least 10 points) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death. • TTCD on the chest pain scale of the QLQ-LC13 scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration (increase of at least 10 points) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death.

BID = twice daily; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; KRAS G12C = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; QD = once a day QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SOC = standard-of-care; TTCD = time to confirmed deterioration.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase III, randomized, active control, open-label study evaluating the efficacy and safety of divarasib versus KRAS G12C inhibitors, sotorasib or adagrasib, in patients with previously treated KRAS G12C + advanced or metastatic NSCLC.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Active comparator	**Population Diagnosis or Condition:**	KRAS G12C-positive advanced or metastatic NSCLC previously treated with standard of care treatments in the advanced or metastatic setting
Interventional Model:	Parallel group	**Population Age:**	≥18 years or older
Test Product{s}:	Divarasib	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Sotorasib or adagrasib	**Study Treatment Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 320

STUDY TREATMENT

Participants in the experimental arm will self-administer divarasib at a dose of 400 mg by mouth (PO) once daily (QD) during each 21-day cycle. The dose of divarasib can be reduced up to two times for management of drug-related toxicities (i.e., from 400 mg to 200 mg and then from 200 mg to 100 mg).

Participants in the control arm will receive either sotorasib or adagrasib. Participants receiving sotorasib will self-administer sotorasib at a dose of 960 mg PO QD during each 21-day cycle. Participants receiving adagrasib will self-administer adagrasib at a dose of 600 mg PO twice a day during each 21-day cycle. Please refer to respective local prescribing information for dose modification guidelines of sotorasib and adagrasib.

DURATION OF PARTICIPATION

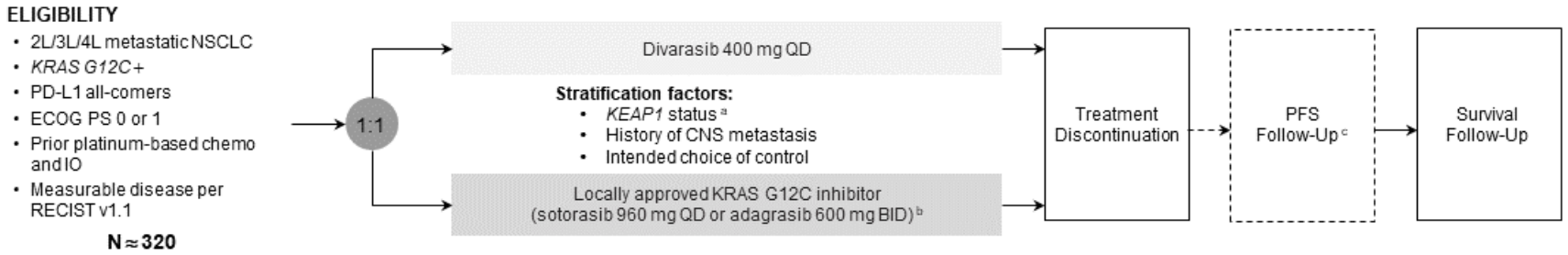
Treatment will continue until disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 or, in the case of participants continuing study treatment beyond progression, until loss of clinical benefit. The total duration of study participation for each individual is expected to range from 1 day to more than 4 years.

COMMITTEES

Independent Committees:	independent Data Monitoring Committee
Other Committees:	Not applicable

1.2 STUDY SCHEMA

Figure 1 Study Design



2L = second-line treatment; 3L = third-line treatment; 4L = fourth-line treatment; BID = twice daily; chemo = chemotherapy; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; F1LCDx = FoundationOne® Liquid CDx assay; IO = immunotherapy; *KEAP1* = Kelch-like ECH-associated protein 1; *KRAS G12C* = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; *KRAS G12C*+ = *KRAS G12C*-mutation positive; NSCLC = non–small cell lung cancer; PD–L1 = program cell death–ligand 1; PFS = progress-free survival; PO = orally; QD = daily; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: To ensure the control arm represents a mix of both control drug options, the Sponsor may slow or pause recruitment at sites if there is a major discrepancy in the distribution of participants receiving either control drugs.

[a] *KEAP1* mutation status will be determined either from central F1LCDx or from preexisting results from Sponsor-approved NGS tests.

[b] Depending on the local approval status, participants randomized to the control arm will receive either sotorasib 960 mg PO QD or adagrasib 600 mg PO BID; if both sotorasib and adagrasib are locally approved at a given site, investigators will choose between sotorasib and adagrasib prior to randomization, with the participant receiving the same drug throughout the duration of the treatment period (i.e., participants who receive sotorasib cannot switch to adagrasib or vice versa).

[c] Participants who discontinue study treatment for reasons other than disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will undergo PFS follow-up until radiographic disease progression, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Day(s) (Window)	Protocol Reference	Screening [a]		Treatment Period (21-Day Cycles)			Treatment Discontinuation [b]	Follow-Up	
				Cycles 1–2		Cycles 3+		PFS Follow-Up	OS Follow-Up
		−28 to −15	−14 to −1	1 [c] (±2) [d]	8 (±2)	1 (±3)	≤28 days after final dose of study treatment	Q6W (±14)	~Q3M (±14)
Informed consent [e]	8	x							
Review of inclusion and exclusion criteria	5.1 5.2	x							
Demographics	8	x							
Medical history and baseline conditions	8	x							
ECOG PS [f]		x		x		x	x		
EORTC QLQ-C30, EORTC QLQ-LC13 [g, h]	8.1.2 Appendix 6			x		x	x	x [i]	x [i]
EuroQol EQ-5D-5L [g, h]	8.9 Appendix 6			x		x	x	x [i]	x [i]
PRO-CTCAE [g, h]	8.2.6 Appendix 6			x	x	x	x		
EORTC IL46 [h, j]	8.2.6			Cycle 2 only	x	x	x		
Vital signs [h, k]	8.2.2		x	x	x	x	x		
Weight		x		x		x	x		
Height		x							
Complete physical examination [l]	8.2.1	x		Cycle 1 only					

Table 1 Schedule of Activities (cont.)

Day(s) (Window)	Protocol Reference	Screening [a]		Treatment Period (21-Day Cycles)			Treatment Discontinuation [b]	Follow-Up	
				Cycles 1–2		Cycles 3+		PFS Follow-Up	OS Follow-Up
		−28 to −15	−14 to −1	1 [c] (±2) [d]	8 (±2)	1 (±3)	≤28 days after final dose of study treatment	Q6W (±14)	~Q3M (±14)
Limited physical examination [h, m]	8.2.1			Cycle 2 only	x	x	x		
Single 12-Lead ECG	8.2.3	x		x		x (every 3 cycles starting at Cycle 3 and as clinically indicated)	x		
Hematology [h]	Appendix 2		x	x	x	x	x		
Chemistry [h, n]	Appendix 2		x	x	x	x	x		
Pregnancy test [h, o]	Appendix 2		x	x		x	x		
Urinalysis [h]	Appendix 2		x		x				
HIV, HBV, and HCV serology	Appendix 2	x							
Lipase [h]		x		x	x	x	x		
Coagulation: INR and aPTT [h]	Appendix 2	x		Cycle 1 only		x (every 3 cycles starting at Cycle 3)	x		
Divarasib administration [p]	6.1.1			x	x	x			
Sotorasib administration [q]	6.1.2			x	x	x			

Table 1 Schedule of Activities (cont.)

Day(s) (Window)	Protocol Reference	Screening [a]		Treatment Period (21-Day Cycles)			Treatment Discontinuation [b]	Follow-Up	
				Cycles 1–2		Cycles 3+		PFS Follow-Up	OS Follow-Up
		−28 to −15	−14 to −1	1 [c] (±2) [d]	8 (±2)	1 (±3)	≤28 days after final dose of study treatment	Q6W (±14)	~Q3M (±14)
Adagrasib administration [r]	6.1.3			x	x	x			
Review of medication diary [h]	6.4			Cycle 2 only		x			
Tumor assessment [s]	8.1.1	x [t]		Every 6 weeks (±7 days) from Day 1 of Cycle 1 for 48 weeks then every 9 weeks (±7 days) thereafter, regardless of treatment delays until radiographic disease progression [u]			x [b]	x [v]	
Plasma PK sample [h]	8.4			Refer to Table 2					
Documentation of *KRAS G12C*-positive status [w]	8.7	x							
Archival or fresh pretreatment tumor tissue specimen for biomarkers [x]	8.7	x							
Blood sample for *KEAP1* mutation status [y]	8.7	Refer to Table 2							
Blood sample for inherited WGS/WES analysis (at participating sites)	8.10.1			Refer to Table 2					

Table 1 Schedule of Activities (cont.)

Day(s) (Window)	Protocol Reference	Screening [a]		Treatment Period (21-Day Cycles)			Treatment Discontinuation [b]	Follow-Up	
				Cycles 1–2		Cycles 3+		PFS Follow-Up	OS Follow-Up
		−28 to −15	−14 to −1	1 [c] (±2) [d]	8 (±2)	1 (±3)	≤28 days after final dose of study treatment	Q6W (±14)	~Q3M (±14)
Blood and plasma sample for biomarkers	8.7			Refer to Table 2					
Optional: Tumor tissue sample for biomarkers [z]	8.10.2						x		
Concomitant medications [h, aa]	6.8	x		x	x	x	x		
Adverse events [h, bb]	8.3 Appendix 3	x		x	x	x	x	x	
Survival and anticancer therapy follow-up [cc]	7.1							x	x

Table 1 Schedule of Activities (cont.)

CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organisation for Research and Treatment of Cancer; F1LCDx = FoundationOne® Liquid CDx assay; FFPE = formalin-fixed, paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; *KEAP1* = Kelch-like ECH-associated protein 1; *KRAS G12C* = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; MRI = magnetic resonance imaging; NGS = next generation sequencing; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; RBR = Research Biosample Repository; WES = whole exome sequencing; WGS = whole genome sequencing.

Notes: On study visit days, all assessments should be performed prior to dosing or initiating the next cycle of study treatment, unless otherwise specified. Refer to the cited protocol reference for activity specific details. Some assessments may be done outside the window indicated to accommodate holidays and unforeseen scheduling issues, with proper documentation in the patient medical records. The investigator should review local laboratory results prior to dosing or initiating the next cycle of study treatment; if the results are questionable, assessments should be repeated immediately. For this purpose, there is a window of ±2 days for Cycle 2 and ±3 days for Cycle 3 and beyond to complete the assessments, unless otherwise specified.

Unscheduled visits may be performed if clinically indicated. The following assessments should be performed at a minimum during any unscheduled visit: concomitant medications and adverse events. Additional assessments (e.g., hematology, chemistry, and ECG) may be performed as clinically indicated, per investigator discretion.

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within 28 days prior to Day 1 of Cycle 1 may be used; such assessments do not need to be repeated for screening. Screening assessments performed within 48 hours of Day 1 of Cycle 1 are not required to be repeated on Day 1 of Cycle 1. A prescreening ICF may be signed and a tumor tissue sample and blood sample may be submitted for *KRAS G12C* and/or *KEAP1* mutation assessment, respectively, before other screening procedures are initiated.

[b] Participants who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 28 days after their final dose of study drug or within 7 days after the decision of treatment discontinuation if it is out of 28 days after the last dose. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Activities required for the treatment discontinuation visit do not need to be repeated if they were performed within 7 days. Tumor assessments do not need to be repeated if one was performed within 28 days of the treatment discontinuation visit.

[c] Participants should receive their first dose of study treatment on the day of randomization if possible, and no later than 4 calendar days after randomization.

[d] The Cycle 1 Day 1 visit and procedures should be completed on the same day if possible; however, some assessments or activities may be performed within 48 hours prior to the Cycle 1 Day 1 initial treatment. A window of ±2 days will be allowed for the completion of the Cycle 2 Day 1 visit.

[e] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained up to 28 days before initiation of study treatment.

[f] ECOG PS assessment may be performed ≤96 hours before Day 1 of each cycle.

Table 1 Schedule of Activities (cont.)

[g] Questionnaires will be self-administered or interviewer-administered (as appropriate) before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment. In scenarios where non-PRO assessments (e.g., blood draws, imaging scans) are completed at a different location than the one providing treatment or are performed on a different day than study treatment administration, the non-PRO assessments can be completed before the completion of PRO questionnaires as long as the results have not been discussed with participants. EORTC QLQ-C30, EORTC QLQ-LC13, EORTC IL46, PRO-CTCAE, and the EuroQol EQ-5D-5L questionnaires will be completed by participants on an electronic device prior to administration of study drug. For questionnaires where the translation is not available in the participant's preferred language, the participant will be exempt from completing the questionnaire until it is available. If it is determined that Day 1 of a given treatment cycle will be delayed after the participant has already completed the PRO questionnaires, the participant should not complete the Day 1 questionnaires for this cycle again. Additionally, the timing of any subsequent PRO assessments will be based on the actual Day 1 of the given cycle (e.g., if it is determined that the start of treatment at Cycle 2 will be delayed a week, the applicable Cycle 2 Day 8 PRO assessments will occur 1 week after the start of treatment, and the Day 1 of Cycle 3 assessment will occur when the next Day 1 administration of treatment is planned).

[h] Starting from Cycle 2 Day 1, for participants at participating sites who have provided written informed consent to participate in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the participant's home.

[i] Questionnaires will be collected 3 and 6 months after treatment discontinuation, regardless of the participant's disease progression. Questionnaires may be completed at home if there are no scheduled site visits that align with the collection timepoints (3 months and 6 months after treatment discontinuation).

[j] For Cycle 1, the EORTC IL46 questionnaire is not administered on Day 1 but on Day 8 only.

[k] Vital signs include temperature, pulse rate, respiratory rate, oxygen saturation, and systolic and diastolic blood pressure while the participant is in a seated position.

[l] A complete physical examination includes, at a minimum, assessments of the assessment of the head and neck, breast or chest wall and regional lymph nodes, and the cardiovascular, dermatologic, respiratory, gastrointestinal, and neurologic systems.

[m] A limited physical examination includes, at a minimum, symptom-directed physical examination. Investigators should pay special attention to clinical signs related to previous serious illnesses.

[n] For participants with recent checkpoint inhibitor exposure (less than 60 days prior to study treatment initiation), more frequent ad hoc liver function tests are advised if there is evidence of elevated liver enzyme or signs and symptoms suggestive of hepatitis as assessed by the investigator.

[o] For all female participants of childbearing potential: a serum pregnancy test must be performed during screening within 7 days of starting Cycle 1. At subsequent timepoints, urine pregnancy tests will be performed. A positive urine test must be confirmed by a serum test.

[p] On clinic visit days when PK samples will be collected (see Table 2), divarasib is to be administered after the PK sample collection at either the clinic or outside of the clinic to ensure the participant can take divarasib at approximately the same time each day. On Day 1 of each cycle, dispense a sufficient number of tablets to the participant to last until the next visit or, at the investigator’s discretion, until the next cycle.

Table 1 Schedule of Activities (cont.)

[q] On clinic visit days when PK samples will be collected (see Table 2), sotorasib is to be administered after the PK sample collection at either the clinic or outside of the clinic to ensure the participant can take sotorasib at approximately the same time each day. On Day 1 of each cycle, participants should receive a prescription for or be supplied with a sufficient number of tablets of sotorasib to last until the next visit or, at the investigator's discretion, until the next cycle.

[r] Adagrasib 600 mg will be administered twice daily. On clinic visit days when PK samples will be collected (see Table 2), the morning dose is to be administered at the clinic after the PK sample collection. On Day 1 of each cycle, participants should receive a prescription for or be supplied with a sufficient number of tablets of adagrsib to last until the next visit or, at the investigator's discretion, until the next cycle.

[s] Tumor assessments must be performed independently of changes to the treatment administration schedule. If a tumor assessment is performed early or late, subsequent assessments should be conducted according to the original schedule based on Day 1 of Cycle 1. All participants must undergo an MRI or CT scan (with contrast) of the brain at screening and at each subsequent tumor assessment. In the event of an equivocal CT scan, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases.

[t] All screening tumor assessments (unless otherwise specified) should be completed within 28 days prior to randomization.

[u] Participants who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments every 6 weeks (±7 days) after initial documentation of progression or more frequently, if clinically indicated, regardless of time in study, until treatment is discontinued. Refer to Section 8.1.1 for more details.

[v] Participants who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity, symptomatic deterioration) will continue to undergo tumor assessments every 6 weeks (±7 days) until radiographic disease progression, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. In the absence of radiographic disease progression, tumor assessments should continue regardless of whether a participant starts a new anticancer therapy.

[w] For all participants enrolled based on preexisting test results, a full, legible, and de-identified report of the molecular test for *KRAS G12C* is required and must be submitted to the Sponsor's central laboratory within 30 days of randomization. If preexisting test results are not available for *KRAS G12C* mutation status, a representative tumor specimen must be submitted during screening or optional prescreening for central assessment of *KRAS G12C* biomarker eligibility. Refer to Section 8.7 for specific tumor specimen requirements.

[x] For all enrolled participants, a mandatory pretreatment tumor specimen is required along with an associated pathology report for biomarker objectives. Tumor tissue samples must be collected before study treatment begins. If a participant has a preexisting test result for *KRAS G12C*, the representative tumor specimen must be confirmed available during screening and submitted to the central laboratory within 30 days of randomization. If a participant has already submitted a pretreatment tumor specimen to centrally assess *KRAS G12C* biomarker eligibility, an additional tumor specimen is not required. Refer to Section 8.7 for specific tumor specimen requirements.

Table 1 Schedule of Activities (cont.)

[y] For all prospective participants with *KRAS G12C*-positive tumors, a blood sample must be sent to the Sponsor's designated NGS diagnostic laboratory for determination of *KEAP1* mutation status using F1LCDx during screening or optional prescreening, even if a prospective participant has a preexisting *KEAP1* mutation test result. While central assessment of *KEAP1* mutation status is preferred for stratification, participants may use preexisting *KEAP1* results from Sponsor-approved NGS tests that are performed at an appropriately accredited/certified laboratory. If central results are available at randomization, participants will be considered to have a *KEAP1* mutation detected if either the central or pre--existing result has a *KEAP1* mutation (detecting a mutation on both tests is not required). For participants stratified on preexisting *KEAP1* test results, the full, legible, and de-identified NGS report (all pages and attachments) must be submitted to the Sponsor's central laboratory within 30 days of randomization. Sponsor-approved NGS tests for *KEAP1* status must have complete exonic coverage of *KEAP1* and report all variants.

[z] Optional tumor biopsy (FFPE tumor tissue samples) will be collected at disease progression from participants who have provided written consent and if collection of tumor biopsy is deemed clinically feasible. If possible, optional fresh tumor biopsies should be obtained within 48 hours of the participant's final dose of study treatment, but no later than 8 weeks from progression assessment and prior to initiation of subsequent anticancer therapy. Tumor biopsy of the growing lesion is preferred. Refer to Section 8.10.2 for specific tumor specimen requirements.

[aa] Includes any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit.

[bb] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention and serious adverse events considered related to Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures) should be reported. After initiation of study treatment, all adverse events will be reported until 28 days after the final dose of study treatment or until initiation of a new anticancer therapy, whichever occurs first. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Appendix 3).

[cc] After treatment discontinuation, information on survival status and new anticancer therapy will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death (unless the participant withdraws consent, is lost to follow-up [see Section 7.3], or the Sponsor terminates the study). If a participant requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the participant withdraws from the study, the study staff may use a public information source (e.g., county records), if allowed by local laws, to obtain information about survival status only.

Table 2 Schedule of Blood-Based Pharmacokinetic and Biomarker Samples

Visit	Timepoint	Sample Type
Prescreening	Any time	Blood for *KEAP1* mutation status [a]
Screening	Days −28 to −1	
Cycle 1 Day 1	Predose	Blood for WGS/WES [b]
		Blood for NGS control
		Plasma for divarasib PK [c]
		Plasma for adagrasib or sotorasib PK [c]
		Blood for biomarkers
		Plasma for safety biomarkers
Cycle 1 Day 8	Any time	Plasma for safety biomarkers
Cycle 2 Day 1 [d]	Predose	Plasma for divarasib PK [c]
		Plasma for adagrasib or sotorasib PK [c]
	Any time	Blood for biomarkers
		Plasma for safety biomarkers
Cycle 2 Day 8 [d]	Any time	Plasma for safety biomarkers
Cycles 3-8 Day 1 [f]	Any time	Plasma for safety biomarkers
Every odd Cycles 3+ Day 1 [d]	Predose	Plasma for divarasib PK [c]
		Plasma for adagrasib or sotorasib PK [c]
	Any time	Blood for biomarkers [e]
Treatment discontinuation	Any time	Plasma for divarsib PK
		Plasma for adagrasib or sotorasib PK
		Blood for biomarkers [f]
Unscheduled visit	As clinically indicated	Plasma for divarasib PK
		Plasma for adagrasib or sotorasib PK

ADA = anti-drug antibody; F1LCDx = FoundationOne® Liquid CDx assay; *KEAP1* = Kelch-like ECH-associated protein 1; NGS = next generation sequencing; PK = pharmacokinetic; WES = Whole Exome Sequencing; WGS = Whole Genome Sequencing.

[a] For all prospective participants with *KRAS G12C*-positive tumors, a blood sample must be sent to the Sponsor's designated NGS diagnostic laboratory for determination of *KEAP1* mutation status using F1LCDx during screening or optional prescreening, even if a prospective participant has a preexisting *KEAP1* mutation test result. While central assessment of *KEAP1* mutation status is preferred for stratification, participants may use preexisting *KEAP1* results from Sponsor-approved NGS tests that are performed at an appropriately accredited/certified laboratory. If central results are available at randomization, participants will be considered to have a *KEAP1* mutation detected if either the central or preexisting result has a *KEAP1* mutation (detecting a mutation on both tests is not required). For participants stratified on preexisting *KEAP1* test results, the full, legible, and de-identified NGS report (all pages and attachments) must be submitted to the Sponsor's central laboratory within 30 days of randomization. Sponsor-approved NGS tests for *KEAP1* status must have complete exonic coverage of *KEAP1* and report all variants.

[b] Not applicable for a site that has not been granted approval for WGS/WES.

[c] Predose plasma PK samples should be collected within 5 minutes prior to dosing but may be obtained up to 2 hours prior to dosing. When the predose PK sample is on a day following divarasib or sotorasib/adagrasib dosing, the exact time of dosing as well as PK draw (clock time) should be noted.

[d] For participants at participating sites who have provided written informed consent to participate in mobile nursing visits, the sample collection(s) for this visit may be performed by a trained nursing professional at the participant's home.

[e] Starting on Cycle 3, blood collection for biomarkers will occur on Day 1 of every odd cycle (Cycle 3, 5, 7, etc.) up to and including Cycle 17 and every 9 weeks thereafter to match tumor assessment visits. Blood collections for biomarkers can occur at any timepoint relative to dosing and are not required to be collected before study drug administration.

[f] Blood collection for biomarkers will occur at treatment discontinuation or disease progression, whichever occurs first.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of divarasib, a KRAS G12C inhibitor, compared to locally approved KRAS G12C inhibitors (sotorasib or adagrasib) in patients with *KRAS G12C*-positive (KRAS G12C+) advanced or metastatic non-small cell lung cancer (NSCLC) who have been previously treated with standard of care treatments in the advanced or metastatic setting. Recently, several KRAS G12C inhibitors have been developed and studied in this patient population; however, the available data to date indicate that an unmet medical need still exists, and that more efficacious KRAS G12C inhibitors with acceptable safety profile and tolerability could improve the long-term outcome for patients.

2.2 BACKGROUND

Lung cancer is the leading cause of cancer death in the world (Sung et al. 2021). Standard first line treatment for advanced or metastatic NSCLC (including KRAS G12C+) includes platinum-based chemotherapy, immunotherapy, or a combination of chemotherapy and immunotherapy. Subsequent treatments include: platinum-based chemotherapy or immunotherapy for patients who had not previously received those therapeutic modalities, docetaxel or other non-specific chemotherapy agents, or a clinical trial (Postmus et al. 2017; National Comprehensive Cancer Network [NCCN] 2024). NSCLC that has been treated with standard of care chemotherapy and/or immunotherapy in the advanced or metastatic setting has a poor prognosis. Genomic and molecular screening for predictive biomarkers has become increasingly important for NSCLC and has transformed patient outcomes (Restrepo et al. 2023). KRAS G12C+ NSCLC represents a genomically distinct subset of the disease for which targeted therapies have recently become available. Patients with KRAS G12C+ NSCLC initially (e.g., first and/or second line) receive similar treatments as patients who have *KRAS G12C*-negative NSCLC in the absence of other actionable driver alterations. For patients with KRAS G12C+ NSCLC, several oral therapies specifically targeting the mutation have been developed and are available in many countries for patients who have received standard first line metastatic NSCLC treatments.

Divarasib (also known as GDC-6036) is an oral, covalent, anticancer therapeutic agent that selectively inhibits only the G12C mutant KRAS receptor. The mixed control arm in this study includes locally approved KRAS G12C inhibitors sotorasib and adagrasib (approvals vary by geographical region), both of which represent an option for patients with previously treated KRAS G12C+ advanced or metastatic NSCLC. Sotorasib (AMG 510) and adagrasib (MRTX849) are small molecules that irreversibly inhibits KRAS G12C by locking it in its inactive guanosine diphosphate-bound state, similar to divarasib. Divarasib has been shown to be 5 to 20 times as potent and up to 50 times as selective in vitro as sotorasib and adagrasib (Purkey 2022). In a Phase I study, divarasib was evaluated in patients with advanced or metastatic cancers, including

60 patients with NSCLC (Sacher et al. 2023). Among the patients with NSCLC, the confirmed response rate was 53.4% (95% CI: 39.9–66.7) and the median progression free survival (PFS) was 13.1 months (95% CI: 8.8–not evaluable), indicating promising clinical anti-tumor activity in a similar patient population to those who will be enrolled in this trial.

Detailed information on divarasib is provided in the Divarasib Investigator's Brochure. Detailed information on sotorasib and adagrasib is provided in the respective local prescribing information.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the efficacy and safety of divarasib, a selective inhibitor of KRAS G12C, to address an unmet medical need in patients with previously treated KRAS G12C+ advanced or metastatic NSCLC. Divarasib will be compared to KRAS G12C inhibitors (sotorasib or adagrasib). In countries where both sotorasib and adagrasib are approved, investigators will have a choice between the two therapies.

Divarasib has been investigated as a monotherapy and in combination with other anticancer therapies at multiple dose levels across several tumor types in a Phase I study (GO42144). In the monotherapy arm of the study, divarasib was found to have promising anticancer activity in patients with KRAS G12C+ solid tumors, including NSCLC, and also demonstrated an acceptable safety profile (Sacher et al. 2023). The important potential risks of gastrointestinal toxicities (diarrhea, nausea, and vomiting), laryngeal irritation, and elevation of hepatic transaminases were monitorable, manageable, and reversible.

Refer to Appendix 4 for information on anticipated risks for divarasib and risk mitigation measures, including guidelines for managing adverse events associated with divarasib.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of divarasib may be found in the Divarasib Investigator's Brochure.

Taking into account the safety and clinical activity data for divarasib in patients with KRAS G12C+ NSCLC, the Sponsor has assessed the benefit–risk profile of single-agent divarasib as the experimental arm of this study (BO45217) to be acceptable.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

This study will evaluate the efficacy and safety of divarasib compared with locally approved KRAS G12C inhibitors (sotorasib or adagrasib) in participants with previously treated KRAS G12C+ advanced or metastatic NSCLC.

3.1 PRIMARY OBJECTIVE AND CORRESPONDING ESTIMANDS

The primary objective for the study expressed using the estimand framework in accordance with the ICH E9(R1) statistical principles for clinical trials (ICH 2020) is described below.

Primary Objective	Estimand Definition
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: Individuals with KRAS G12C+ advanced or metastatic NSCLC who have received at least one prior systemic therapy • Endpoint: PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) • Treatment: – Experimental arm: divarasib 400 mg QD – Control arm: KRAS G12C inhibitor (sotorasib 960 mg QD or adagrasib 600 mg BID), depending on investigator's choice, as applicable • Intercurrent events and handling strategies: – Early discontinuation from study treatment: treatment policy strategy – Start of non-protocol specified anticancer therapy prior to disease progression: treatment policy strategy • Population-level summary: hazard ratio for PFS

BID = twice daily; KRAS G12C = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; NSCLC = non-small cell lung cancer; PFS = progression-free survival; QD = once a day; RECIST = Response Evaluation Criteria in Solid Tumors; SOC = standard-of-care.

3.2 SECONDARY OBJECTIVES AND CORRESPONDING ESTIMANDS AND ENDPOINTS

The key secondary objectives for the study are expressed using the estimand framework in accordance with the ICH E9(R1) statistical principles for clinical trials (ICH 2020). Other secondary objectives and corresponding endpoints are described below.

Key Secondary Objectives	Estimand Definitions
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: As defined above for PFS • Endpoint: OS, defined as the time from randomization to death from any cause • Treatment: As defined above for PFS • Intercurrent events and handling strategies: – Early discontinuation from study treatment: treatment policy strategy – Start of non-protocol specified anticancer therapy: treatment policy strategy • Population-level summary: hazard ratio for OS
• To evaluate, from the participant's perspective, the functioning and impact of key disease-related symptoms of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: As defined above for PFS • Endpoint: TTCD on the EORTC QLQ-C30 dyspnea item and the physical functioning scale, and the cough scale of the QLQ-LC13 scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration (decrease from baseline in the functioning scale of at least 10 points or increase in the symptom scales of at least 10 points) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death. • Treatment: As defined above for PFS • Intercurrent events and handling strategies: – Early discontinuation from study treatment prior to a confirmed clinically meaningful deterioration: treatment policy strategy – Start of non-protocol specified anticancer therapy prior to a confirmed clinically meaningful deterioration: hypothetical strategy – Death that occurs before participants report any clinically meaningful deterioration: while-alive strategy • Population-level summary: hazard ratio for TTCD
Other Secondary Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• ORR, defined as the proportion of participants with a CR or PR, as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first)

Other Secondary Objectives	Corresponding Endpoints
• To evaluate the safety and tolerability of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 grading scale • Change from baseline in selected vital signs and ECG parameters • Change from baseline in selected clinical laboratory test results • Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne) as assessed through use of the NCI PRO-CTCAE • Change from baseline in diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne as assessed through use of the NCI PRO-CTCAE • Frequency of participants' response of the degree they are troubled with treatment symptoms, as assessed through use of the single-item EORTC Item List (IL46)
• To evaluate the quality of life of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Change from baseline in cough, chest pain, dyspnea, physical and role functioning, and GHS/QoL at each timepoint as assessed through use of the EORTC QLQ-LC13 and QLQ-C30 • TTCD on the EORTC QLQ-C30 role functioning and GHS/QoL scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration (decrease from baseline of at least 10 points) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death. • TTCD on the chest pain scale of the QLQ-LC13 scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration (increase of at least 10 points) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death.

CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; KRAS G12C = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TTCD = time to confirmed deterioration.

3.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Exploratory objectives and corresponding endpoints are described below.

Exploratory Objectives	Corresponding Endpoints
• To assess the CNS activity of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Cumulative incidence rates of CNS progression as determined by the investigator according to RECIST v1.1, at 6 and 12 months • Time to CNS progression as determined by the investigator according to RECIST v1.1, defined as the time from randomization until first radiographic evidence of CNS progression • Intracranial PFS as determined by the investigator according to RECIST v1.1, defined as the time from randomization until first radiographic evidence of CNS progression or death from any cause (whichever occurs first)
• To characterize pharmacokinetics of divarasib	• Plasma concentration of divarasib at specified timepoints
• To characterize pharmacokinetics of sotorasib	• Plasma concentration of sotorasib at specified timepoints
• To characterize pharmacokinetics of adagrasib	• Plasma concentration of adagrasib at specified timepoints
• To evaluate potential relationships between drug exposure and the efficacy and safety of divarasib	• Relationship between plasma concentration or PK parameters for divarasib and efficacy endpoints • Relationship between plasma concentration or PK parameters for divarasib and safety endpoints
• To evaluate potential relationships between selected covariates and exposure to divarasib	• Relationship between selected covariates and plasma concentration or PK parameters for divarasib

Exploratory Objectives	Corresponding Endpoints
• To identify and/or evaluate biomarkers that are predictive of response to divarasib compared with KRAS G12C inhibitors (sotorasib and adagrasib) (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to divarasib compared with KRAS G12C inhibitors, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of divarasib activity (i.e., pharmacodynamic biomarkers) compared with KRAS G12C inhibitors, or can increase the knowledge and understanding of disease biology and drug safety or pharmacokinetics	• Relationship between biomarkers in blood, plasma, and tumor tissue (listed in Section 8.7) and efficacy, safety, PK, or other biomarker endpoints
• To evaluate and compare participants' health status to generate utility scores for use in economic models for reimbursement	• Health status, as assessed by the EuroQol EQ-5D-5L questionnaire

CNS = central nervous system; KRAS G12C = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase III, randomized, active control, open-label study evaluating the efficacy and safety of divarasib versus KRAS G12C inhibitors, sotorasib or adagrasib, in patients with previously treated KRAS G12C+ advanced or metastatic NSCLC.

Approximately 320 participants will be randomized in a 1:1 ratio to receive either divarasib 400 mg by mouth (PO) once daily (QD) (experimental arm) or a locally approved KRAS G12C inhibitor (control arm). Depending on the local approval status, participants randomized to the control arm will receive either sotorasib 960 mg PO QD or adagrasib 600 mg PO twice daily (BID); if both sotorasib and adagrasib are locally approved at a given site, investigators will choose between sotorasib and adagrasib prior to randomization, with the participant receiving the same drug throughout the duration of

the treatment period (i.e., participants who receive sotorasib cannot switch to adagrasib or vice versa). The proportion of participants receiving each control drug will be monitored by the Sponsor.

To ensure the control arm represents a mix of both control drug options, the Sponsor may slow or pause recruitment for one of the drugs if there is a major discrepancy in the distribution of participants receiving either control drugs.

Randomization will be stratified by *KEAP1* mutation status (mutation detected or not detected/unknown) determined by the Sponsor's designated testing laboratory or preexisting results from Sponsor-approved tests, history of CNS metastasis (yes or no), and intended KRAS G12C inhibitor in the control arm (sotorasib or adagrasib). Unknown results for *KEAP1* are not allowed for preexisting NGS tests.

Participants should receive the first dose of study treatment on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 4 calendar days after randomization. The assigned study treatment will continue until progression of disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, intolerable adverse events, withdrawal of consent, death, or Sponsor termination, whichever occurs first. Participants who discontinue study treatment prior to radiographic progression of disease according to RECIST v1.1 will continue to have tumor assessments, even if they start new anticancer therapy, according to the schedule of activities (Section 1.3) until progression of disease according to RECIST v1.1, withdrawal of consent, lost to follow-up, death, or Sponsor termination.

The primary objective will be evaluated using radiographic assessments of the tumor according to RECIST v1.1 at the frequency specified in the schedule of activities (Section 1.3).

The study includes a screening period of up to 28 days, a treatment period, and a long-term follow-up period for PFS and overall survival (OS). Participants who discontinue study treatment for reasons other than disease progression will undergo PFS follow up until documentation of progression of disease, withdrawal of consent, lost to follow-up, death, or discontinuation of the study. After confirmed disease progression, participants from the PFS follow-up will enter survival follow-up. All participants who discontinue study treatment will be followed for OS from the safety follow-up until death, withdrawal of consent from the study, lost to follow-up, or termination of the study by the Sponsor.

In order to obtain information for eligibility and stratification for this study, *KRAS G12C* mutation testing for eligibility and/or *KEAP1*-mutation testing for stratification may be performed as prescreening ahead of the screening period. Prescreening is optional and not mandatory for study participation but may expedite screening activities. Participants will be required to sign a separate informed consent form to participate in prescreening.

The prescreening testing(s) will be performed in tumor tissue for *KRAS G12C* mutations (only for participants without a preexisting result) and blood sample for *KEAP1* mutations (only for participants whose tumors are KRAS G12C+ as determined by preexisting results or during this prescreening period).

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities and a sample collection schedule are provided in Section 1.3 (see Table 1 and Table 2).

Imaging data used for tumor assessments by the investigator will be collected to enable a blinded independent central review (BICR) of response endpoints, if needed. An independent review facility (IRF) may review all available (de-identified) radiographic tumor assessments to assess tumor response according to RECIST v1.1. Details of the IRF's responsibilities and procedures will be specified in a separate IRF charter, if applicable.

An independent Data Monitoring Committee (iDMC) will be established to conduct periodic reviews of aggregate safety data. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the frequency of the reviews, the summary of the data, and their roles and responsibilities.

4.1.1 Treatment after Disease Progression

Participants experiencing clinical benefit in the judgment of the investigator while receiving study treatment may continue study treatment beyond disease progression (as defined by RECIST v1.1) at the investigator's discretion, if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of signs and symptoms indicative of unequivocal progression of disease (including worsening of laboratory values [e.g., new or worsening hypercalcemia])
- No decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Written consent from participants to acknowledge deferring alternative treatment options in favor of continuing study treatment at the time of initial progression

4.1.2 Patient Input into Study Design

Representatives from an organization within the patient community were interviewed and asked to provide feedback on the following aspects of the study:

- Study design, endpoints, inclusion and exclusion criteria activities, and patient-reported outcome (PRO) assessments

- Recruitment and retention

This feedback was taken into consideration when developing the protocol.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

This study will be conducted in patients with advanced or metastatic NSCLC that harbors a *KRAS G12C* mutation and have received prior systemic therapies for advanced or metastatic disease. *KRAS G12C* is a well-established oncogenic driver mutation and defines a distinct subgroup of NSCLC with a prevalence of approximately 12% (varies by region/race). Patients with KRAS G12C+ NSCLC that have progressed after standard therapies have limited treatment options and a generally poor prognosis. Recently, specific targeted inhibitors of KRAS G12C have been developed, providing a more personalized treatment option for this NSCLC biomarker defined subset. All of the study drugs used in this study are specific inhibitors of KRAS G12C. The control drug(s) for this study has been approved for use in this patient population in the countries participating in this study.

4.2.2 Rationale for Control Arm

This is a concurrent active treatment control study evaluating the efficacy and safety of divarasib compared to locally approved therapies within the same therapeutic class of oral KRAS G12C inhibitors. The intent of this study is to demonstrate a difference between the experimental arm of the study (divarasib) and the mixed control arm of approved KRAS G12C inhibitors (sotorasib or adagrasib). The currently available nonclinical and clinical data support evaluating whether divarasib can improve on the efficacy established by therapies, with an acceptable safety and tolerability profile.

The control arm of this study includes locally approved KRAS G12C inhibitors. Sotorasib 960 mg PO QD has been approved for previously treated KRAS G12C+ NSCLC in several countries across the globe. In many countries, sotorasib has become a standard-of-care treatment option given that it has demonstrated a statistically significant increase in PFS when compared to cytotoxic chemotherapy (de Langen et al. 2023). Sotorasib also represents an oral option with a favorable tolerability profile compared to the alternative of cytotoxic chemotherapy, which is administered every three weeks via intravenous infusion. Adagrasib 600 mg PO BID is also a specific KRAS G12C inhibitor that has been approved in several countries and represents a standard-of-care option for patients previously treated with standard therapies (Jänne et al. 2022). Based on the available data published to date, sotorasib and adagrasib are considered clinically similar in regard to efficacy (sotorasib PFS: 5.6–6.8 months; adagrasib median PFS: 6.5 months) (Skoulidis et al. 2021; Jänne et al. 2022; de Langen et al. 2023), and multinational treatment guidelines recommend either as an acceptable treatment option for the disease setting in which this trial will be conducted (Hendriks et al 2023; NCCN 2024). The approval status and use of sotorasib and

adagrasib also varies by country. While the drugs have the same mechanism of action and have similar clinical efficacy, they are not considered interchangeable, and physicians take a number of patient and clinical factors into consideration when choosing which KRAS G12C inhibitor to use in countries where both are approved. Therefore, in a global clinical trial aiming to enroll a representative patient population with KRAS G12C+ advanced or metastatic NSCLC, it is clinically appropriate to include a mixed control arm of both of the approved in class alternatives.

4.2.3 Rationale for Open-Label Design

An open-label design was selected due to the technical and practical complexities that would be faced in blinding the IMPs. There is a significant difference in the number of tablets required each day for each IMP (refer to Table 3 for more details). Given the large variation in required number of tablets per day, combined with one of the control options being dosed twice daily (as opposed to once daily), a blinded study would involve participants taking a high number of placebo tablets per day, which could have an impact on quality of life and the patient experience on the trial. Further, while all three study drugs have similar mechanisms of action, there are important differences in the toxicity and drug interaction profiles, adverse event management, and use of concomitant medications, which are drug-specific. Blinding of treatments in this scenario would place undue burden on both participants and investigators.

In order to provide a technically feasible and patient-centric approach, with lower risk of non-compliance, medication errors, and suboptimal management of study treatment toxicities, adequate steps have been taken to ensure the validity of data in an open-label study design. This includes performing efficacy assessments at the same frequency in both arms, adhering to protocol-defined schedules, and determining the strategy for the final analysis of the primary endpoint prior to study start, including predefined methods for handling missing data and censoring rules. Well established disease assessment criteria will be used uniformly across all arms of the study (RECIST v1.1). The study is also powered to test for overall survival. Efficacy analyses will only be performed at the prespecified analysis timepoints in the protocol (primary analysis once the number of PFS events presented in Section 9.1.1 have occurred in the full analysis set [see Section 9.2]). The Sponsor will not review aggregated efficacy data by treatment arm prior to release of Treatment Assignment Information data.

4.2.4 Rationale for Biomarker Assessments

NSCLC is a biologically heterogeneous disease. Therefore, all participants may not be equally likely to benefit from treatment with divarasib. Blood, plasma, and tissue samples will be assessed for predictive biomarkers in an effort to identify those participants with KRAS G12C+ tumors who are most likely to respond to divarasib. In addition, pharmacodynamic biomarkers will be assessed in blood samples to demonstrate evidence of biologic activity of divarasib in participants. As these

biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

Whole genome sequencing (WGS) or whole exome sequencing (WES) of blood and tissue samples will be conducted to identify somatic variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. DNA extracted from blood or PBMCs will be compared with DNA extracted from tissue to distinguish somatic variants from germline variants. Genomics is increasingly informing researcher's understanding of disease pathobiology. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

In this study, archival or fresh NSCLC tumor tissue samples from participants without preexisting *KRAS G12C* positive test results will be submitted for *KRAS G12C* mutation status testing by a central laboratory through the use of the investigational Qiagen therascreen *KRAS* RGQ PCR assay. The Qiagen therascreen *KRAS* RGQ PCR assay is an U.S. Food and Drug Administration (FDA)-approved companion diagnostic for sotorasib, which received accelerated approval for the treatment of adult patients with KRAS G12C+ advanced or metastatic NSCLC, who have received at least one prior systemic therapy. Testing may be performed during the optional prescreening or screening period to assess biomarker eligibility. If an archival tumor tissue sample is unavailable or determined to be unsuitable for the required *KRAS G12C* testing, participants may undergo a biopsy at prescreening or screening if the investigator deems it safe and clinically feasible. When archival tumor specimens are used for *KRAS G12C* testing, there is no additional risk from a biopsy for a prospective participant with regard to use of the investigational Qiagen therascreen *KRAS* RGQ PCR assay. Prospective participants undergoing a biopsy to provide a freshly collected tumor specimen for the use of the investigational Qiagen therascreen *KRAS* RGQ PCR assay may incur additional non-serious risks from the biopsy.

Pre-treatment blood samples will also be collected from all prospective *KRAS G12C*+ participants for *KEAP1* mutation status testing by a Sponsor-designated laboratory during the optional prescreening or screening period. This study may enroll individuals with *KRAS G12C*+ NSCLC regardless of *KEAP1* mutation status; however, participants will be stratified by *KEAP1* status (mutation detected vs. not detected/unknown) through central use of the FDA approved Foundation Medicine FoundationOne® Liquid CDx (F1LCDx) assay or preexisting results from Sponsor-approved NGS tests that are performed at appropriately accredited/certified laboratories (unknown results for *KEAP1* are not allowed if using preexisting NGS tests). As a blood sample will be collected using minimally invasive sampling procedures, there is minimal risk to a prospective participant with regard to the use of Foundation Medicine F1LCDx assay.

4.2.5 Rationale for Stratification Factors

To ensure balance during randomization, *KEAP1* mutation status, history of CNS metastasis, and intended KRAS G12C inhibitor in the control arm will be used as stratification factors.

KEAP1 mutations are suggested to have a potential prognostic impact on clinical outcomes in patients with NSCLC (Papillon-Cavanagh et al. 2020; Hellyer et al. 2021), and they frequently co-occur with *KRAS G12C* mutations in NSCLC (Arbour et al. 2018). In retrospective analyses, co-mutations in *KRAS G12C* and *KEAP1* have been correlated with reduced overall response rates, PFS, and OS compared to *KRAS G12C, KEAP1* wildtype tumors in patients with NSCLC treated with KRAS G12C inhibitors (Skoulidis et al. 2021; Jänne et al. 2022; Sacher et al. 2023; Negrao et al. 2023a). Prospectively stratifying by *KEAP1* mutation status will minimize the risk of imbalance of this poor prognostic biomarker and prevent *KEAP1*-related confounding effects on the comparison of divarasib's clinical activity to sotorasib's or adagrasib's.

Randomization will also be stratified by history of CNS metastasis. CNS involvement is common in KRAS G12C+ advanced NSCLC, occurring in 27–42% of patients (Cui et al. 2020; Sebastian et al. 2021; Wu et al. 2021; Spira et al. 2021), and is associated with a poor prognosis (Parikh et al. 2015; Tomasini et al. 2016; Lauko et al. 2021). Sotorasib and adagrasib have been evaluated in a limited number of patients with untreated or treated brain metastases, and these analyses indicate some evidence of intracranial activity (Ramalingam et al. 2021, Negrao et al. 2023b). However, the intracranial activity of KRAS G12C inhibitors has not been completely characterized. Therefore, stratifying based on history of CNS metastasis will mitigate the potential for imbalance among participants receiving divarasib and participants receiving the control drugs.

In addition to the stratification factors of *KEAP1* mutation status and history of CNS metastasis, randomization will be stratified by the intended KRAS G12C inhibitor that the participant will receive if randomized to the control arm. Although the mixed control arm includes two drugs with the same mechanism of action (KRAS G12C inhibition) and similar efficacy (Skoulidis et al. 2021; Jänne et al. 2022), there are key differences in the

adverse event profile and drug interaction profile that may influence an investigator's choice when selecting between the two (Corral de la Fuente et al. 2022; Lumykras® [sotorasib] Summary of Product Characteristics [SmPC]; Krazati® [adagrasib] SmPC). Furthermore, certain clinical characteristics such as a history of brain metastases, may also have an impact on selection of the control drug (Reck et al. 2021; Riely et al. 2021). Stratifying by intended KRAS G12C inhibitor will allow for balanced subgroups between the participants receiving the individual control drugs and the participants receiving divarasib.

4.2.6 Rationale for Collection of Information on Race and Ethnicity

Data pertaining to participant race and ethnicity represents a component of the broad demographic profile of the study population. Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial, including identification of potential differences in efficacy, safety, and pharmacokinetics among participants. Collection of race and ethnicity data may enable investigation of potential relationships between biomarkers and race or ethnicity, including determination of whether race or ethnicity could be a prognostic factor. Collection of these data may also contribute to a better understanding of the distribution of NSCLC according to race or ethnicity.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

Based on the totality of nonclinical data, clinical safety and activity data, and analyses of clinical exposure–response relationships, including exposure–efficacy and exposure–safety, 400 mg QD of divarasib has been selected for further evaluation in this study. Nonclinical studies with divarasib demonstrate that anti-tumor activity is dependent on the extent of divarasib covalent target engagement, inhibition of the KRAS pathway, and the intrinsic dependence on KRAS G12C in a given tumor context. Less sensitive nonclinical models demonstrate that higher doses of divarasib are required to achieve maximal covalent target engagement and sustained inhibition of cell proliferation, both of which are necessary to achieve anti-tumor activity. Together, these nonclinical data suggest that higher clinical exposures of divarasib capable of maximizing covalent target engagement and inhibition of cellular proliferation may benefit a higher proportion of patients.

From Study GO42144, the observed mean minimum concentration under steady-state conditions ($C_{min,ss}$) in participants treated with 400 mg QD of divarasib was greater than the exposure required to achieve maximal covalent target engagement based on nonclinical models. Based on the $C_{min,ss}$ derived from the preliminary population pharmacokinetic (PK) model, a larger proportion of patients treated with 400 mg QD of divarasib, compared with 200 mg QD, 100 mg QD or 50 mg QD, is predicted to achieve exposures corresponding to maximal covalent target engagement from nonclinical studies. Consistent with the nonclinical data, an analysis of exposure–response showed that a higher $C_{min,ss}$ was correlated with a higher probability of achieving disease control

(defined as stable disease or better) and appeared to be associated with a higher probability of partial response (PR) in participants with NSCLC. Common adverse events reported with divarasib, including nausea, vomiting, and diarrhea of any grade, and Grade 3 events did not appear to have a relationship with divarasib dose or exposure. Based on analysis of exposure–adverse event relationships, there was no significant correlation between steady state exposure for maximum concentration observed (C_{max}), area under the concentration–time curve (AUC), or minimum concentration observed (C_{min}) and the probability of adverse events, including Grade ≥ 2 nausea, vomiting, diarrhea, and ALT and/or AST increased. Furthermore, anti-tumor activity with divarasib as a single agent has been observed at all dose levels evaluated across tumor types, including in NSCLC. In conclusion, the exposure-safety and exposure-efficacy analyses suggest that the 400 mg QD divarasib dose provides better activity without compromising safety compared to lower doses.

In the KRAS G12C+ cohort of Study BO29554 (Blood First Assay Screening Trial), participants were randomized to 200 and 400 mg QD divarasib cohorts to evaluate the pharmacokinetics, safety, tolerability, and anti-tumor activity of divarasib. Preliminary data from a pre-specified interim analysis continued to support 400mg QD divarasib as the selected dose for evaluation in this study.

Overall, the available nonclinical and clinical data for divarasib support the further evaluation of 400 mg QD of divarasib in this study.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last scheduled procedure shown in the schedule of activities (see Section 1.3, Table 1).

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last data point required for statistical analysis (i.e., PFS and OS) or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur more than 4 years after the last participant is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

Treatment will continue until disease progression per RECIST v1.1 or, in the case of participants continuing study treatment beyond progression, until loss of clinical benefit. The total duration of study participation for each individual is expected to range from 1 day to more than 4 years.

5. STUDY POPULATION

Approximately 320 participants with previously treated KRAS G12C+ NSCLC will be enrolled in this study.

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

5.1 INCLUSION CRITERIA

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

- Signed Informed Consent Form
- Age ≥ 18 years at the time of signing Informed Consent Form
- Unequivocal histologically or cytologically confirmed diagnosis of unresectable Stage IIIc, per the American Joint Committee on Cancer staging system (AJCC) (Amin et al. 2017) not amenable to treatment with combined modality chemoradiation (advanced) or Stage IV (metastatic) NSCLC
- Disease progression during or after treatment with at least one prior systemic therapy but no more than three lines of prior systemic therapy in the metastatic setting (with the exceptions for adjuvant/neoadjuvant therapies as outlined below):
  - Prior systemic treatment must include a platinum-based doublet chemotherapy regimen and a PD-L1/PD-1 inhibitor, either given in combination as one line of therapy (i.e., PD-L1/PD-1 inhibitor plus platinum-based doublet chemotherapy) or as individual lines of therapy (i.e., PD-L1/PD-1 inhibitor preceded or followed by platinum-based doublet chemotherapy) unless the individual has a medical contraindication to one of the required therapies. Approved PD-L1/PD-1 inhibitors must have been administered according to local drug prescribing information.
  - Adjuvant/neoadjuvant platinum-based chemotherapy, adjuvant platinum-based chemotherapy followed by immunotherapy, chemoradiation, or chemoradiation followed by immunotherapy qualifies as a prior systemic therapy if < 6 months have elapsed between the last dose and the date of recurrence.
  - If a participant has additional approved standard treatment options available, the study doctor must offer these additional approved treatment options and discuss the risks and benefits of those treatments with the participant before informed consent to participate in this study is obtained. This discussion must be documented in patient records.
- Measurable disease according to RECIST v1.1
- Documentation of the presence of a *KRAS G12C* mutation through central laboratory testing of a tumor tissue sample or preexisting test results of a blood or tumor tissue sample

  - Preexisting test results in blood or tumor tissue for *KRAS G12C* must be performed using a validated PCR or next-generation sequencing (NGS) assay from an appropriately accredited/certified laboratory (e.g., Clinical Laboratory Improvement Amendments-certified or equivalent). The full legible and de-identified laboratory report of the *KRAS G12C* mutation result must be available and submitted to the Sponsor's designated central laboratory within 30 days of randomization.
  - Participants without preexisting test results for *KRAS G12C* mutation status must submit a representative tumor tissue sample at the time of screening or optional prescreening for central assessment of biomarker eligibility. Central *KRAS G12C* assessment will be done in accordance with local regulations.
- Determination of *KEAP1* mutation status using the Sponsor's designated NGS diagnostic laboratory and test (F1LCDx) or from preexisting results from Sponsor-approved NGS tests
  - Blood samples will be collected from all prospective participants with KRAS G12C+ tumors for central assessment of *KEAP1* mutation status, even if a prospective participant has a preexisting *KEAP1* result. While central assessment of *KEAP1* mutation status is preferred for stratification, participants may use preexisting test results from Sponsor-approved NGS tests that are performed at an appropriate accredited/certified laboratory. The full, legible, and de-identified NGS report (all pages and attachments) must be submitted to the Sponsor's designated central laboratory within 30 days of randomization. Unknown *KEAP1* results from preexisting NGS tests are not allowed.
  - If central results are available at the time of randomization, participants will be considered to have a *KEAP1* mutation detected if either the central or local preexisting result has a *KEAP1* mutation (detecting a mutation on both tests is not required).
  - Sponsor-approved NGS test for *KEAP1* status must have complete exonic coverage of *KEAP1* and report all variants.
- Availability of a representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or 10–15 (15 preferred) unstained, freshly cut, serial slides with an associated pathology report
  - If <10 slides are available, the participant may be eligible for the study following consultation with the Sponsor (see Section 8.7 for tumor tissue requirements).
  - The mandatory tumor tissue sample must be confirmed as available during screening and shipped to the central laboratory within 30 days of randomization (if not already sent during screening or optional prescreening for central assessment of biomarker eligibility).
  - If archival tumor tissue is unavailable or determined to be unsuitable for required testing, participants may undergo a biopsy at prescreening or screening if the investigator deems it safe and clinically feasible. A biopsy may also be performed at screening for central assessment of biomarker eligibility if a participant's archival tumor tissue test results do not meet eligibility criteria.

Refer to Section 8.7 for additional information on collection and analysis of screening samples.

- ECOG Performance Status of 0 or 1
- Life expectancy of ≥ 12 weeks
- Adequate hematologic and organ function within 14 days prior to initiation of study treatment, defined by the following:
  - ANC $\geq 1500/\mu L$ with one exception:

    Participants with benign ethnic neutropenia (BEN) may be eligible: ANC $\geq 1.3 \times 10^9/L$ (1300/μL) BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestations (Atallah-Yunes et al. 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.
  - Hemoglobin ≥ 9 g/dL without transfusion
  - Platelet count $\geq 100{,}000/\mu L$ without transfusion
  - Total bilirubin $\leq 1 \times$ upper limit of normal (ULN)
  - Serum albumin ≥ 2.5 g/dL
  - Liver function tests meeting one of the following criteria:
    - AST and ALT $\leq 2.5 \times$ ULN, with ALP $\leq 2.5 \times$ ULN

      or
    - AST and ALT $\leq 1.5 \times$ ULN, with ALP $> 2.5 \times$ ULN

      Patients with documented liver metastases may have AST and/or ALT $\leq 5.0 \times$ ULN.
  - Creatinine clearance ≥ 45 mL/min on the basis of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

    An online calculator for the creatinine clearance using the CKD-EPI equation can be found at the following website: https://www.mdcalc.com/calc/3939/ckd-epi-equations-glomerular-filtration-rate-gfr
  - INR $< 1.5 \times$ ULN and aPTT $< 1.5 \times$ ULN

    This applies only to individuals who are not receiving therapeutic anticoagulation. Individuals receiving therapeutic anticoagulation should be on a stable dose for at least 1 week prior to Day 1 of Cycle 1.
- Negative HIV test at screening with the following exception: individuals with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count $\geq 200/\mu L$, and have an undetectable viral load
- Negative hepatitis B surface antigen (HbsAg) test at screening

- Positive hepatitis B surface antibody (HbsAb) test at screening, or a negative HbsAb at screening accompanied by either of the following:
  - Negative hepatitis B core antibody (HbcAb)
  - Positive HbcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) DNA test

  The HBV DNA test must be performed for individuals who have a negative HbsAg test, a negative HbsAb test, and a positive HbcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or a positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test must be performed for individuals who have a positive HCV antibody test.
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception and agree to refrain from donating eggs as defined below:

  Female participants must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 7 days after the final dose of sotorasib, or 6 months after the final dose of divarasib or adagrasib.

  Participants must refrain from donating eggs during this same period.

  A female participant is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

    Please see Section 6.8.2.2 and the local prescribing label for sotorasib for information regarding potential drug–drug interactions (DDI) between this drug and hormonal contraceptives.

  For participants receiving sotorasib, hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate

methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, male participants must remain abstinent or use a condom during the treatment period and for 7 days after the final dose of sotorasib, 4 months after the final dose of divarasib or 6 months after the final dose of adagrasib to avoid exposing the embryo. Male participants must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

5.2 EXCLUSION CRITERIA

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

- Pregnancy or breastfeeding, or intention of becoming pregnant during the study or within 7 days after the final dose of sotorasib, or 6 months after the final dose of divarasib or adagrasib.

  Female participants of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

- Known hypersensitivity to any of the components of divarasib, or sotorasib or adagrasib
- Inability to comply with study and follow-up procedures
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Known concomitant second oncogenic driver (including sensitizing *EGFR* mutations, *ALK* rearrangement, *ROS1* rearrangement, *BRAF V600E* mutation, *HER2* mutations, *NTRK* fusions, *RET* fusions, *MET Exon 14* skipping mutations)

  Testing for listed mutations is not required to determine eligibility.

- Mixed small-cell lung cancer or large cell neuroendocrine histology
- Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control)

Participants with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:

  - Measurable disease outside the CNS
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - No ongoing requirement for corticosteroids as therapy for CNS metastases, with corticosteroids discontinued for ≥ 2 weeks prior to enrollment and no ongoing symptoms attributed to CNS metastases
  - No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to Day 1 of Cycle 1
  - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

Note: Participants with new asymptomatic CNS metastases detected at screening are eligible for the study after receiving radiotherapy and/or surgery. Following treatment, these participants may be eligible without the need to repeat the additional brain scan, if all other criteria are met.

- Leptomeningeal disease or carcinomatous meningitis
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures biweekly or more frequently

  Indwelling pleural or abdominal catheters are allowed regardless of drainage frequency, provided the participant has adequately recovered from the procedure, is hemodynamically stable, and symptomatically improved
- Any infection that, in the opinion of the investigator, could impact patient safety, or treatment with therapeutic oral or IV antibiotics within 14 days prior to Day 1 of Cycle 1

  In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).
- Clinically significant history of liver disease, including viral or other hepatitis, or cirrhosis
- Hypercalcemia (ionized calcium >1.5 mmol/L or calcium >12 mg/dL) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination findings, or clinical laboratory findings that give reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or renders the participant at high risk from treatment complications
- Significant traumatic injury or major surgical procedure within 4 weeks prior to Day 1 of Cycle 1

- Chronic diarrhea, short bowel syndrome, or significant upper gastrointestinal surgery including gastric resection, a history of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) or any active bowel inflammation (including diverticulitis)
- Prior treatment with any KRAS G12C inhibitor or pan-KRAS/RAS inhibitor
- Treatment with anticancer therapy (e.g., chemotherapy, immunotherapy, biologic therapy, or an investigational anticancer agent) within 3 weeks prior to initiation of study treatment.
- More than 30 Gy of radiotherapy to the lung within 6 months of randomization
- Uncontrolled tumor-related pain
  - Participants requiring pain medication must have adequate pain control.
  - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to randomization. Participants should be recovered from the effects of radiation. There is no required minimum recovery period.
  - Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for locoregional therapy, if appropriate, prior to randomization.
- Unresolved toxicities from prior anticancer therapy, defined as not having resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Grade 1 or better, or to levels dictated in the eligibility criteria or toxicities from prior anticancer therapy or palliative radiation therapy that are considered irreversible (defined as having been present and stable for $>$6 months)

  Exceptions of unresolved toxicities include alopecia, vitiligo, or endocrinopathy managed with replacement therapy
- Treatment with strong CYP3A4 inhibitors or inducers (see Section 6.8.2.1) within 14 days or 5 half-lives of the drug or its major active metabolite, whichever is longer, prior to initiation of study treatment
- Any serious medical condition or abnormality in clinical laboratory tests that precludes an individual's safe participation in and completion of the study
- Blood or platelet transfusion within 14 days prior to screening
- History or presence of an abnormal ECG that is deemed clinically significant, (e.g., complete left bundle branch block, second- or third-degree atrioventricular heart block) or evidence of prior myocardial infarction
- History of malignancy within 5 years prior to screening, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$90%), such as adequately treated carcinoma in situ of the cervix, nonmelanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer

- Significant cardiovascular disease, as evidenced by any of the following conditions within 6 months of randomization:
  - QT interval corrected through the use of Fridericia's formula (QTcF) $>$480 ms demonstrated by at least two ECGs $>$30 minutes apart.
  - Has clinically significant, uncontrolled, cardiovascular disease, including Grade III or IV congestive heart failure according to the New York Heart Association classification; myocardial infarction or unstable angina within the previous 6 months, uncontrolled hypertension, or clinically significant, uncontrolled arrhythmias, including bradyarrhythmias that may cause QT prolongation (e.g., Type II second-degree or third-degree heart block)
- History of prolonged QT syndrome or torsades de pointes
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval (Appendix 9)

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has the following meal and dietary restrictions:

- Refrain from consumption of grapefruit, grapefruit juice, pomelo, or Seville oranges from 7 days before the start of study treatment until after the final dose

5.3.2 Caffeine, Alcohol, and Tobacco

The study has the following alcohol restrictions:

- From screening until completion of the study, participants will drink no more than two servings of alcohol per day (one serving is 12 ounces of beer, 5 ounces of wine, 1.5 ounces of spirits, or equivalent). Participants must agree to abstain from alcohol consumption 12 hours prior to Day 1 of Cycle 1.

This study has no caffeine or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion. Individuals are not required to re-sign the consent form if they are re-screened within 14 days after previously signing the consent form. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

The investigational medicinal products (IMP) for this study are divarasib, sotorasib, and adagrasib. Appendix 10 identifies all investigational medicinal products for this study.

6.1 STUDY TREATMENT ADMINISTERED

Table 3 provides a description of assigned study treatments for this study.

Table 3 Study Treatment Description

	Divarasib	Sotorasib	Adagrasib
Use	Experimental	Active comparator	Active comparator
Drug form	Tablet	Tablet	Tablet
Unit dose strength(s)	25 mg, 50 mg, 100 mg, 200 mg, 400 mg	120 mg	200 mg
Dosage level	400 mg QD	960 mg QD	600 mg BID
Formulation	Refer to pharmacy manual and Divarasib Investigator's Brochure	Refer to local prescribing information	Refer to local prescribing information
Packaging	25 tablets per bottle		
Labeling	Per local requirements		
Route of administration	Oral	Oral	Oral
Source	Sponsor	Sponsor or site [a]	

BID = twice daily; QD = daily.

[a] In the US, sotorasib and adagrasib may be provided by the Sponsor centrally or via patient pharmacy cards, or locally by the site.

The treatment regimens are summarized in Section 4.1.

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 4.

6.1.1 Divarasib

Participants will self-administer divarasib at a dose of 400 mg PO QD during each 21-day cycle (see Section 4.1). For divarasib doses to be administered at home, a sufficient number of tablets should be dispensed to the participant to last until the next visit, or at the investigator's discretion, through one 21-day cycle. Participants will self-administer divarasib at home or in the clinic on specific clinic visit days as detailed below.

Participants should take divarasib at approximately the same time each day unless otherwise instructed. Participants should be instructed on proper pill swallowing without chewing or crushing the tablet. A minimum of 240 mL (8 ounces) of water should be taken with divarasib. Divarasib tablets can be taken with or without food. Participants will be instructed as to the number and strength of tablets to take. Participants will be asked to record the time and date that they take each dose in a medication diary.

During clinic visits when PK sampling is scheduled, participants will be instructed to hold the dose of divarasib if the time that the participant would take divarasib is prior to or during the clinic visit, until after blood samples have been obtained for PK and laboratory assessments. After the sample collection, the participants can take divarasib either at the clinic or outside of the clinic to ensure divarasib is taken at approximately the same time each day.

If a participant misses any dose of divarasib (not taken within 6 hours after scheduled dosing time) or vomits up a tablet, he or she should be instructed to skip that dose, document it in the participant's medication diary, and resume dosing with the next scheduled dose. Missed doses will not be made up.

Participants will be instructed to bring their medication diary to each study visit for assessment of compliance. Participants will also be instructed to bring all unused tablets to each study visit or, at the investigator's discretion, at the end of each cycle, for drug accountability.

6.1.2 Sotorasib

Participants will receive sotorasib 960 mg PO QD during each 21-day cycle. Participants will self-administer sotorasib at home or in the clinic on specific clinic visit days as detailed below.

Participants should take the sotorasib dose whole (all tablets at the same time) with or without food at approximately the same time every day.

During clinic visits when PK sampling is scheduled, participants will be instructed to hold the dose of sotorasib if the time that the participant would take sotorasib is prior to or during the clinic visit, until after blood samples have been obtained for PK and laboratory assessments. After the sample collection, the participants can take sotorasib either at

the clinic or outside of the clinic to ensure sotorasib is taken at approximately the same time each day.

A medication diary will be provided for participants to record their adherence to the oral medication.

The sotorasib dose should not be taken more than 2 hours earlier or more than 6 hours later than the scheduled time (based on the previous day's dose). If a participant misses a dose of sotorasib and if less than 6 hours have passed since the scheduled timing of the dosing, the participant should take the dose as normal. If more than 6 hours have passed since the scheduled time of dosing, the participant must not take the dose. Treatment should be continued as prescribed the next day. Missed doses will not be made up.

If vomiting occurs after taking sotorasib, the participant must not take an additional dose on the same day, and should document it in the medication diary and continue treatment as prescribed the next day.

For more details regarding sotorasib administration, refer to the local prescribing information for sotorasib.

6.1.3 Adagrasib

Participants will receive adagrasib 600 mg PO BID during each 21-day cycle. Participants will self-administer adagrasib at home as detailed below, except on specific clinic visit days where participants will be instructed to take their morning dose of adagrasib in the clinic after all predose assessments have been performed.

A mediation diary will be provided for participants to record their adherence to the oral medication.

Adagrasib should be taken at the same time every day with or without food. The tablet should be swallowed whole without chewing, crushing, or splitting the tablet.

If vomiting occurs after taking adagrasib, the participant must not take an additional dose and should document it in the medication diary and resume dosing at the next scheduled time. If a dose is inadvertently missed and more than 4 hours have elapsed from the scheduled dosing time, it should be skipped. The participant should resume dosing at the next scheduled time. Missed doses will not be made up.

For more details regarding adagrasib administration, refer to the local prescribing information for adagrasib.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor where required by local regulations. The study site (i.e., investigator or other authorized personnel e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using an interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. Temperature conditions for all IMPs will be monitored during transit, and any discrepancies will be reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor if supplied by the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Divarasib Investigator's Brochure or local sotorasib or adagrasib prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS.

Participants will be randomly assigned to one of two treatment arms: divarasib or locally approved KRAS G12C inhibitor (sotorasib or adagrasib). Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced

assignment to each treatment arm. Randomization will be stratified by *KEAP1* mutation status, history of CNS metastasis, and intended KRAS G12C inhibitor in the control arm (see Section 4.1 for details).

6.4 STUDY TREATMENT COMPLIANCE

When participants self-administer study treatment, compliance will be assessed.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

The dose of divarasib can be reduced up to two times for management of drug-related toxicities, as described in Appendix 4.

Please refer to respective local prescribing information for dose modification guidelines of sotorasib and adagrasib.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to Roche IMP (divarasib) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMP (divarasib) after completing the study if all of the following conditions are met:

- The participant received Roche IMP during study conduct.
- The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

Eligible participants will be provided access to Roche IMP for up to 3 years after completing the study, unless mandated otherwise by local regulations.

A participant will not be eligible to receive Roche IMP (divarasib) after completing the study if any of the following conditions are met:

- The participant was assigned to a treatment arm that did not include a Roche IMP during study conduct.

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for NSCLC.
- The Sponsor has reasonable safety concerns regarding the IMP as a treatment for NSCLC.
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until the study treatment can no longer be detected systemically (at least 5 days for divarasib; in accordance with institutional guidelines for sotorasib and adagrasib).
3. If requested by the Medical Monitor (determined on a case-by-case basis), obtain a sample for PK analysis within 5 days from the date of the last dose of study treatment for divarasib and in accordance with institutional guidelines for sotorasib and adagrasib.

6.8 CONCOMITANT THERAPY

Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit must be recorded on the Concomitant Medications eCRF(s) along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2.

Use of the following concomitant therapies is permitted as described below:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Sections 6.8.2.2 for additional information regarding potential DDI between hormonal contraceptives and sotorasib).
- Hormone-replacement therapy
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) or surgery as outlined below:
  - In participants without documentation of radiographic disease progression, it is strongly encouraged to maximize supportive care for symptomatic management and to avoid radiotherapy that will interfere with the assessment of tumor target lesions. The need for radiotherapy is generally considered indicative of progressive disease, and the Medical Monitor should be notified if palliative radiotherapy is planned or started.
  - For participants receiving divarasib, interrupt dosing with divarasib 2 days in advance of radiation therapy or surgery and resume dosing 2 days after completion of radiation therapy or recovery from surgery.
  - For participants receiving sotorasib, if he or she requires palliative radiotherapy or surgery during the study, the Sponsor must be informed before therapy initiation at the earliest opportunity. Sotorasib should be paused until after completion of the treatment and for 7 days post-completion of radiation. Resuming the study drug is contingent upon a discussion between the Medical Monitor and the investigator to ascertain the suitability of treatment continuation.
  - For participants receiving adagrasib, in the event that major surgery is needed during study treatment, the participant should, if possible, interrupt dosing with adagrasib 2 weeks in advance of the surgery and resume dosing 2 weeks after completion of the surgery.
- Pain medications administered per standard clinical practice
- Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed when used to prevent skeletal events. Participants on oral bisphosphonate therapy should be without signs of esophagitis.
- Anti-emetic medications may be administered prophylactically before initial treatment with study drugs.

  - For participants receiving divarasib, ondansetron and similar agents in this class are effective anti-emetic medications based on early clinical experience; prochlorperazine and/or metoclopramide may be effective anti-emetic medications in some participants.
  - For participants receiving sotorasib or adagrasib, refer to the local prescribing information for concomitant administration with anti-emetic medications.
- Anti-diarrheal medications as outlined below:

  Anti-diarrheal medications should not be prophylactically administered prior to initial treatment but may be administered as needed after study treatment initiation. Anticipatory anti-diarrheal medication, such as loperamide, should be provided to study participants (i.e., ensuring participants have access to anti-diarrheal medications if they develop symptoms of diarrhea at home).
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular weight heparin)
  - For participants receiving adagrasib, refer to Section 6.8.2.3 and the local prescribing information for concomitant administration with anticoagulation therapy.
- Vaccinations (such as influenza, COVID-19)

6.8.2 Cautionary Therapy

6.8.2.1 Medications Given with Precaution due to Effects Related to Divarasib

In vitro data suggest that CYP3A4/5 and non-CYP-mediated metabolism may play a significant role in divarasib clearance. Thus, any medication that strongly inhibits or induces this enzyme should be used with caution, including the medications listed below. Divarasib has been shown to induce CYP3A4 mRNA but not protein in vitro. Additionally, in vitro studies using human hepatocytes revealed that M21 (a major circulating metabolite of divarasib; see Divarasib Investigator's Brochure for more details) has the potential to induce CYP3A4 mRNA expression and enzymatic activity. Since a potential DDI due to CYP3A4 induction cannot be ruled out, any medication that is primarily metabolized by this enzyme (i.e., a sensitive CYP3A4 substrate) and for which small changes in exposure may lead to therapeutic failure should be used with caution, including the medications listed below. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with divarasib.

- Strong/moderate CYP3A4 inhibitors, including, but not limited to, the following: atazanavir, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, telithromycin, erythromycin, troleandomycin, fluconazole, itraconazole, ketoconazole, voriconazole, posaconazole, aprepitant, conivaptan, fluvoxamine, diltiazem, nefazodone, mibefradil, verapamil

- Strong/moderate CYP3A4 inducers, including, but not limited to, the following: rifampin, carbamazepine, phenytoin, oxcarbazepine, phenobarbital, efavirenz, nevirapine, etravirine, modafinil, hyperforin (St. John's Wort), and cyproterone

CYP3A4 substrates sensitive to induction, including, but not limited to, the following: alfentanil, budesonide, buspirone, felodipine, everolimus, hormonal contraceptives, lovastatin, quetiapine, sildenafil, simvastatin, sirolimus, tacrolimus

Based on in vitro assays, divarasib was shown to be a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. The effects of P-gp and BCRP modulators on divarasib pharmacokinetics are not known. Any medication that is an inhibitor or inducer of P-gp or BCRP should be used with caution.

- Inhibitors of P-gp: amiodarone, clarithromycin, cobicistat, cyclosporine, dronedarone, erythromycin, itraconazole, ketoconazole, lapatinib, lopinavir and ritonavir, quinidine, ranolazine, saquinavir and ritonavir, verapamil
- Inducers of P-gp: apalutamide, carbamazepine, fosphenytoin, lorlatinib, phenytoin, rifampin, St. John's wort
- Inhibitors of BCRP: curcumin, cyclosporine A, eltrombopag

Based on in vitro assays, divarasib was shown to inhibit P-gp and BCRP transporters. -DDI potential with co-administered P-gp, and BCRP substrates cannot be excluded. Any medication that is an exclusive substrate of P-gp or BCRP with a narrow therapeutic index should be used with caution. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with divarasib.

The above lists of medications are not necessarily comprehensive, refer to the FDA online resource for additional examples at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise if questions arise regarding medications not listed above.

6.8.2.2 Medications Given with Precaution due to Effects Related to Sotorasib

Avoid co-administration of sotorasib with CYP3A4 substrates with narrow therapeutic indices, including but not limited to alfentanil, cyclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus, and tacrolimus.

Co-administration of sotorasib with a proton pump inhibitor or an H2 receptor antagonist leads to a decrease in sotorasib concentrations. If co-administration of sotorasib with an acid-reducing agent (proton pump inhibitor, H2 receptor antagonist) is required,

sotorasib should be taken with an acidic beverage (such as cola). Alternatively, sotorasib should be taken 4 hours before or 10 hours after administration of a local antacid.

When sotorasib is co-administered with medicinal products metabolized by CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6, appropriate monitoring is recommended.

When sotorasib is co-administered with a BCRP substrate, including but not limited to rosuvastatin, monitor for adverse reactions of the BCRP substrate and refer to the BCRP substrate's local prescribing information for additional details.

Co-administration of sotorasib with P-gp substrates with narrow therapeutic indices is not recommended.

Co-administration of sotorasib with strong CYP3A4 inducers is not recommended because they may decrease sotorasib exposure.

For additional and more complete details regarding potential drug interactions, please refer to the local prescribing information for sotorasib.

6.8.2.3 Medications Given with Precaution due to Effects Related to Adagrasib

Avoid concomitant use of adagrasib with strong CYP3A4 inducers.

Avoid concomitant use of adagrasib with strong CYP3A4 inhibitors until adagrasib concentrations have reached steady state (after approximately 8 days).

Avoid concomitant use of adagrasib with sensitive CYP3A substrates unless otherwise recommended in the local prescribing information for these substrates.

Avoid concomitant use of adagrasib with sensitive CYP2C9 substrates where minimal concentration changes may lead to serious adverse reactions.

Avoid concomitant use of adagrasib with sensitive CYP2D6 substrates where minimal concentration changes may lead to serious adverse reactions.

Avoid concomitant use of adagrasib with P-gp substrates where minimal concentration changes may lead to serious adverse reactions.

Avoid concomitant use of adagrasib with other products with a known potential to prolong the QT interval (see Appendix 9).

For additional and more complete details regarding potential drug interactions, please refer to the local prescribing information for adagrasib.

6.8.2.4 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential DDIs are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, for various time periods prior to starting study treatment, depending on the agent (see Section 5.2), and during study treatment, until disease progression is documented and the participant has discontinued study treatment with the exception of palliative radiotherapy, radiotherapy to the brain, and local therapy under certain circumstances (see Section 6.8.1 for details)

For additional information regarding medications that are contraindicated with sotorasib or adagrasib, please refer to the local prescribing information.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. Refer to the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment,
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Use of an anticancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression

- Confirmed disease progression per investigator assessment according to RECIST v1.1 (unless study treatment is continued beyond radiographic progression)
- For participants treated beyond radiographic disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 4.1 for details)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants will return to the clinic for a treatment discontinuation visit ≤28 days after the final dose of study drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Participants who discontinue study treatment for any reason other than progressive disease per RECIST v1.1 will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see Section 1.3).

After treatment discontinuation, information on survival status and new anticancer therapy will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death (unless the participant withdraws consent or the Sponsor terminates the study).

Refer to the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, a treatment discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

If a participant withdraws from the study, the study staff may use a public information source (e.g., county records), if allowed by local laws, to obtain information about survival status.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (e.g., complete blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history will be recorded at screening. Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity at each scheduled or unscheduled visit; treatment decisions will be made according to the clinical assessment and local laboratory test values.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the participant's home to improve access and convenience for participants participating in the study. The Sponsor will select a health-care company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Section 1.3) will specify the assessments that may be performed by an MN professional.

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Participants will undergo tumor assessments at screening, every 6 weeks (±7 days) for the first 48 weeks following treatment initiation (Day 1 of Cycle 1), and every 9 weeks (±7 days) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 (see Appendix 8), loss of clinical benefit as determined by the investigator, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Thus, tumor assessments are to continue according to schedule in participants who discontinue treatment for reasons other than disease progression, even if they start new anticancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Participants who are treated beyond disease progression per investigator-assessed RECIST v1.1 will undergo tumor assessments every 6 weeks (±7 days) after initial documentation of progression, or more frequently if clinically indicated, regardless of time in the study until treatment is discontinued (see Section 4.1 for details).

All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined in Section 8.1.1.1.

8.1.1.1 Radiographic Assessments

Screening and subsequent assessments must include computed tomography (CT) scans with contrast (per institutional standard operating procedures) of the chest and abdomen. A CT scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. If a CT scan with contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and magnetic resonance imaging (MRI) scans (with contrast, if feasible) of the abdomen and pelvis should be performed. CT or MRI scans of other disease sites should be performed as clinically indicated.

The use of radiopharmaceutical products (e.g., ^{18}F-FDG, Tc-99m, MIBG) and contrast agents (e.g., gadolinium-based or iodinated contrast media) in study imaging assessments will be consistent with standard/local practice and will not involve a route of administration, dose, patient population, or any other factor that significantly increases the risk (or decreases the acceptability of the risk) to participants. The products employed in these procedures will be at the discretion of participating investigators and shall be locally authorized or otherwise used in compliance with local regulations. The results of this study will not be used to support any new indication or change in labeling for these products.

All participants must undergo an MRI or CT scan (with contrast) of the brain at screening and as part of each subsequent tumor assessment. In the event of an equivocal CT scan, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases. Participants with active or untreated CNS metastases are not eligible for the study (see Section 5.2). If previously irradiated brain lesions are categorized as non-target lesions, the lesions should be followed at all subsequent tumor assessments.

At the investigator's discretion, other methods of assessment of disease as per RECIST v1.1 may be used. If a CT scan for tumor assessment is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. Further investigations, such as bone scans and CT scans of the neck, should also be performed if clinically indicated.

All measurable and/or evaluable lesions identified at screening should be re-assessed at subsequent tumor evaluations according to the schedule described above. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Tumor assessments must be continued after disease progression per RECIST v1.1 for participants who receive treatment beyond progression at the frequency described above. The investigator's assessment of overall tumor response at all timepoints should be based on RECIST v1.1 only. Results must be reviewed by the investigator before dosing at the next cycle.

Details regarding imaging procedures will be provided in an imaging manual.

Radiographic images will be collected and sent to an IRF for a quality and completeness check, for potential blinded independent central review (BICR), and for temporary storage prior to transferring images to the Sponsor for the long term retention and eventual secondary/exploratory use.

Radiographic images, whether reviewed locally or centrally, must be evaluated by a qualified, certified expert.

8.1.1.2 Response Evaluation

PFS will be calculated programmatically by the Sponsor on the basis of investigator assessments of response at specified timepoints according to RECIST v1.1 (see Appendix 8). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

Other endpoints (e.g., duration of response [DOR] and objective response rate [ORR]), will be calculated programmatically by the Sponsor on the basis of investigator assessments of response at each specified timepoint.

8.1.2 Clinical Outcome Assessments

Patient-reported outcome (PRO) instruments will be completed to assess the treatment benefit of divarasib compared with sotorasib and adagrasib. In addition, PRO instruments will enable the capture of each participant's direct experience with divarasib compared with sotorasib, and adagrasib.

PRO data will be collected through use of the following instruments: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-LC13 (Appendix 6).

8.1.2.1 EORTC QLQ-C30

The QLQ-C30 is a validated, reliable self-reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix 6). It consists of 30 questions that assess five aspects of participant functioning (physical, emotional, role, cognitive, and social), three symptom scales (Fatigue, Nausea and Vomiting, and Pain), global health status (GHS) and quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The QLQ-C30 module takes approximately 10 minutes to complete.

8.1.2.2 EORTC QLQ-LC13

The QLQ-LC13 (see Appendix 6) is a self-reported patient reported outcome (PRO) measure. It is composed of 13 lung cancer specific items and includes 11 disease-specific scales and items (dyspnea, coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts, pain medication; Bergman et al. 1994). The QLQ-LC13 has a recall period of 7 days. All 13 items are scored on a 4-point scale that ranges from "not at all" to "very much." The QLQ-LC13 takes approximately 5 minutes to complete.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head and neck, breast or chest wall and regional lymph nodes, and the cardiovascular, dermatologic, respiratory, gastrointestinal, and neurologic systems.

A limited physical examination will include, at a minimum, symptom-directed physical examination. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from abnormalities identified at screening should be recorded in participant notes. New or worsened clinically significant abnormalities i.e., beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF. Limited physical examinations may be performed by an MN professional.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities, i.e., beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Vital signs will include temperature, respiratory rate, pulse rate, oxygen saturation, and systolic and diastolic blood pressure while the participant is in a seated position.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Vital sign measurement may be performed by an MN professional.

8.2.3 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints (see Table 1) and may be obtained at unscheduled timepoints as clinically indicated.

All ECG recordings must be performed on a device that is equipped with reliable, automated algorithms for measuring heart rate and ECG intervals and capable of local printing. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Lead placement should be as consistent as possible. ECG recordings should be performed after the participant has been resting in a supine position for at least 10 minutes, and the participant should remain in a supine position during recording. The same positioning should be maintained for each participant throughout the study. ECG recordings should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be performed within 2.5 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

Paper copies of all ECG tracings must be reviewed, annotated to indicate any clinical findings, signed, and dated by a medically qualified member of the site staff. For each timepoint, heart rate, RR interval, PR interval, QRS interval, uncorrected QT interval, and QTcF based on machine readings of ECG tracings should be recorded on the

appropriate eCRF. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

If at a particular postdose timepoint the mean QTcF is >500 ms or >60 ms longer than the baseline value (i.e., last value prior to initiation of study treatment), another ECG must be recorded, ideally within the next 5 minutes, and ECGs should be repeated at least hourly until two successive ECGs show resolution of the findings. A PK sample should be obtained if not already scheduled for that timepoint. Guidelines for management of increases in QT interval are provided in Appendix 4.

8.2.4 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Sample collection may be performed by an MN professional.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.2.6 Clinical Outcome Assessments

PRO instruments will be completed to more fully characterize the safety profile of divarasib compared with sotorasib and adagrasib. In addition, PRO instruments will enable the capture of each participant's direct experience with divarasib compared with sotorasib and adagrasib.

PRO data will be collected through use of the following instruments: Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) and EORTC Item List 46 (IL46).

8.2.6.1 PRO-CTCAE

The PRO-CTCAE is a validated item library that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of 12 symptoms deemed most applicable to the current study treatments has been selected for this study (see Appendix 6). Symptoms have been selected on the basis of toxicities associated with the drug class, mechanism of action, or mode of administration and known side effects of divarasib, sotorasib, and adagrasib.

8.2.6.2 EORTC IL46

The IL46 is a single question that assesses bother (burden) of treatment. It is rated on a 1 to 4 scale, ranging from "not at all" to "very much." Similarly worded items have been shown to be a valid and useful summary measure of overall adverse event reporting (Pearman et al. 2018). The single-item IL46 question assesses overall side-effect impact.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study treatment, serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) and serious adverse events considered related to

Qiagen therascreen *KRAS* RGQ PCR assay (including any device-related procedures) should be reported immediately (i.e., no more than 24 hours after the investigator becomes aware of the event). In addition, during this period, non-serious adverse events considered related to Qiagen therascreen *KRAS* RGQ PCR assay (including any device-related procedures) should be reported within 5 days after the investigator becomes aware of the event (see Section A3-5). All other medical events occurring in participants during this period are considered preexisting medical conditions and should be recorded as described in Section A3–7.8. All adverse events will be recorded from the start of treatment until 28 days after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available. Non-serious adverse events considered related to Qiagen therascreen *KRAS* RGQ PCR assay (including any device-related procedures) will be reported within 5 days after the investigator becomes aware of the event.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

The investigator will be informed of any device deficiencies detected at the testing site that might have an impact on clinical study participants (e.g., a test result leading to inappropriate participant management decision). This will enable the investigator to assess for and report any adverse events associated with the device deficiency (see Appendix 3).

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), Institutional Review Boards or Ethics Committees (IRBs/Ecs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Divarasib	Divarasib Investigator's Brochure
Sotorasib	Sotorasib E.U. Summary of Product Characteristics
Adagrasib	Adagrasib E.U. Summary of Product Characteristics

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Divarasib

Investigator's Brochure and Summary of Product Characteristics and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 5. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.6)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- Grade ≥ 3 nausea or vomiting, or diarrhea
- Grade ≥ 3 stomatitis or mucositis
- Grade ≥ 3 hepatitis or elevation in ALT or AST

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 4.

8.3.9 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Plasma samples will be used to evaluate the pharmacokinetics of divarasib as specified in the schedule of activities (see Section 1.3). Samples collected for analyses of divarasib concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Plasma samples may be used to evaluate the pharmacokinetics of adagrasib and sotorasib as specified in the schedule of activities (see Section 1.3). Predose and 2-hour post-dose concentration data of adagrasib and sotorasib may be analyzed based on the totality of data. Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

Refer to Section 8.7 and Appendix 7 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood samples for determination of *KEAP1* mutation status for participant stratification purposes and may include biomarker assay development

  Analysis of *KEAP1* mutation status will be performed using the Foundation Medicine F1LCDx assay for stratification purposes in participants whose tumors are found to be *KRAS G12C*-positive.

- Blood and plasma samples for exploratory biomarker objectives, including translational research and biomarker assay development
- Archival or freshly collected tumor tissue sample obtained at baseline for determination of *KRAS G12C* mutation status for determining biomarker eligibility and exploratory biomarker objectives, including translational research and biomarker assay development

  A representative FFPE tumor specimen in a paraffin block (preferred) or 10−15 slides (15 preferred) containing unstained, freshly cut, serial sections along with an associated pathology report are required for all participants enrolled on study. Although 10 slides are required, if <10 slides are available, the participant may be eligible for the study following consultation with the Sponsor.

  If participants do not have preexisting results for *KRAS G12C* mutational status, the mandatory tumor tissue specimen must be submitted during optional prescreening or screening for central biomarker assessment of eligibility via the Qiagen therascreen *KRAS* RGQ PCR assay. For participants enrolled based on preexisting test results for *KRAS G12C* mutation status, the mandatory tumor tissue sample must be confirmed available during screening and shipped to the central laboratory within 30 days of randomization.

  Tumor tissue should be of good quality, as determined on the basis of total and viable tumor content. Samples must contain a minimum of 500 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core -needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Endobronchial ultrasound (EBUS)-transbronchial needle aspiration is acceptable (particularly if a larger needle is used), provided tissue is of good quality as described above (i.e., minimum number of 500 viable tumor cells with preserved cellular context and tissue architecture). For EBUS-needle aspirations, an 18-guage or larger needle is recommended. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, the participant may undergo a biopsy during screening or prescreening if the biopsy site is safely accessible and deemed clinically feasible. A pre-treatment tumor biopsy may also be performed if an individual's archival tissue test results do not meet eligibility criteria.

Central analysis of *KRAS G12C* mutation status will be performed using the Qiagen therascreen *KRAS* RGQ PCR assay, an FDA-approved and CE Marked In Vitro Diagnostic device, which may be considered investigational per local regulations.

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.10.

Biomarker research may include, but will not be limited to, analysis of ctDNA levels, analysis of copy number and mutational analyses of cancer-related genes, gene signatures associated with tumor cancer biology, immunobiology and drug activity (like MAPK pathway suppression), changes in cytokines and analysis of other safety biomarkers, potential predictive biomarkers of response and mechanisms of resistance. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of gene and/or protein expression, analysis of mutations, copy number, single nucleotide polymorphisms, and other genomic variants; and genomic profiling. Blood samples may be processed to obtain PBMCs and their derivatives (e.g., DNA or RNA).

Genomic research with a focus on somatic variants may be conducted by comparing DNA extracted from blood or PBMCs with DNA extracted from tissue to distinguish somatic variants from germline variants. Genomic profiling may include WGS or WES of tissue, plasma, and blood samples, with a focus on somatic variants. WGS or WES of blood samples with a focus on germline variants may also be conducted, but only at participating sites (see Section 8.10.1).

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator may obtain an NGS report through Foundation Medicine's web portal. If permitted by local law, the investigator may share and discuss the results with the participant, unless the participant chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. The report may be included in the participant’s medical record. Results will not be available for samples that do not meet criteria for testing.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 1 and Table 2). Sample collection may be performed by an MN professional. Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for any remaining blood, plasma, PBMCs, and tumor tissue samples to be stored for optional exploratory research (see Section 8.10.3), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the following exceptions:

- For enrolled participants, remaining archival tissue blocks will be returned to the site upon request or no later than completion of the final Clinical Study Report, whichever occurs first. For individuals who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants unless required by law with the exception of the report from Foundation Medicine. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

8.9.1 EuroQol EQ-5D-5L

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 6). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale that measures health state. The EQ-5D-5L is designed to capture a participant's current health status. Published weighting systems allow for the creation of a single composite score of the participant's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.10.1 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing with a Focus on Germline Variants (Participants at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event

monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will include exploration of germline variants.

The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 8.10.1) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant’s medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Appendix 1).

8.10.2 Tumor Biopsies (Participants Providing Separate Consent)

Consenting participants will undergo an optional tumor biopsy at the time of disease progression (if deemed clinically feasible by the investigator). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. If an optional biopsy is performed, the FFPE tumor specimen in a paraffin block (preferred) or 10 slides containing unstained, freshly cut, serial sections along with an associated pathology report should be submitted. Tumor tissue should be of good quality based on total and viable tumor content. Samples must have greater than 20% tumor content with preserved cellular context and tissue architecture.

The Informed Consent Form will contain a separate section that addresses optional biopsies. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of undergoing optional biopsies. Participants will be told that they are free to choose not to undergo optional biopsies and may withdraw their consent at any time and for any reason. A separate, specific signature will be required to document a participant's agreement to undergo optional biopsies. Participants who choose not to undergo optional biopsies will not provide a separate signature. The investigator should document whether or not the participant has given consent to undergo optional biopsies and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

Samples may be used for exploratory biomarker research as described in Section 8.7. Tumor specimens may be used for centralized retrospective assessment to evaluate correlation between genes, proteins, DNA, and RNA relevant to the signaling pathways associated with sensitivity/resistance to the investigational agents. NGS may be performed by Foundation Medicine on disease progression biopsies. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 8.7 for information on duration of sample storage and availability of data from biomarker analyses.

8.10.3 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.10.3.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.3.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10.3) will not be applicable at that site.

8.10.3.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to divarasib, diseases, or drug safety:

- Any remaining blood, plasma, PBMCs, and tumor tissue (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.3.4 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.3.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period.
A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.3.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples (i.e., all biological material) will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.3.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed

Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The purpose of this study is hypothesis testing, testing superiority of divarasib compared with the locally approved KRAS G12C inhibitors with respect to PFS. The null (H_0) and alternative (H_1) hypotheses regarding PFS in the FAS will be tested at a two-sided significance level of 0.05 and can be phrased in terms of the population hazard ratio (HR) λ between the experimental arm and the control arm:

$$H_0: \lambda = 1 \text{ versus } H_1: \lambda \neq 1$$

Null and alternative hypotheses of a similar form will be tested for the key secondary efficacy analyses for OS and time to confirmed deterioration (TTCD). All hypothesis tests will be two-sided unless stated otherwise.

To control the overall level of significance at a two-sided error rate of 0.05, comparisons with respect to PFS, OS, and TTCD will be conducted hierarchically as follows:

- The primary endpoint PFS will be tested first at an overall two-sided α level of 0.05. If the two-sided p-value corresponding to the stratified log-rank test is less than 0.05, the null hypothesis will be rejected, and it will be concluded that divarasib prolongs duration of PFS relative to sotorasib and adagrasib.
- If divarasib significantly prolongs PFS, then OS will be tested at an overall two-sided α level of 0.05. One interim OS analysis will be performed at the time of the primary PFS analysis. For example, if the two-sided p-value corresponding to the stratified log-rank test is less than 0.0137 at the interim analysis or less than 0.0453 at the final analysis, the null hypothesis will be rejected, and it will be concluded that divarasib prolongs duration of OS relative to sotorasib and adagrasib. Stopping boundaries will be adjusted depending on the actual number of OS events.

  If divarasib has no significant effect on PFS, then OS will not be tested.
- If divarasib significantly prolongs OS, then TTCD will be tested at an overall two-sided α level of 0.05 at the time of the interim OS analysis, or at the time of final OS analysis for selected scales in the following hierarchical order (each scale tested only if preceding scale was tested statistically significant):
  - Cough (EORTC QLQ-LC13)
  - Dyspnea (EORTC QLQ-C30)
  - Physical functioning (QLQ-C30)

For each scale, if the two-sided p-value corresponding to the stratified log-rank test is less than 0.05, the null hypothesis will be rejected, and it will be concluded that divarasib prolongs duration of TTCD relative to sotorasib and adagrasib for this scale.

If divarasib has no significant effect on OS at the interim and at the final OS analyses, then TTCD will not be tested.

9.1.1 Sample Size Determination

A total of approximately 320 participants will be enrolled in this study and randomized in a 1:1 ratio to either divarasib or locally approved KRAS G12C inhibitor (sotorasib or adagrasib). The sample size is determined by the primary endpoint, PFS, and the key secondary endpoint, OS.

The enrollment is projected to complete approximately 14 months after randomization of the first participant with a peak recruitment rate of 32 participants per month. An annual dropout rate of 10% for both arms is assumed. On that basis, it is projected that the primary PFS analysis will occur approximately 24 months after randomization of the first participant and that the final OS analysis will occur approximately 47 months after randomization of the first participant.

The estimates of the number of events required to demonstrate efficacy with regards to PFS are based on the following assumptions:

- Two-sided significance level of 0.05
- 90% power to detect a hazard ratio of 0.64, corresponding to an improvement in median PFS from 7 months to 10.9 months
- The primary analysis of PFS will be conducted when approximately 216 PFS events are observed.
- Under these assumptions, the minimal detectable difference will be a hazard ratio of 0.766 corresponding to an improvement in median PFS from 7 months to approximately 9.1 months.

The estimates of the number of events required to demonstrate efficacy with regard to OS are based on the following assumptions:

- Two-sided significance level of 0.05
- 80% power to detect a hazard ratio of 0.69, corresponding to an improvement in median OS from 13 months to 18.8 months
- One interim analysis for OS at the time of the primary PFS analysis (when approximately 66% of the total OS events have occurred), with use of the Lan-DeMets approximation to the O'Brien-Fleming boundaries (for details see Section 9.4)

- The final OS analysis will be conducted when approximately 231 OS events are observed.
- Under these assumptions, the minimal detectable difference at the final OS analysis will be a hazard ratio of 0.769 corresponding to an improvement in median OS from 13 months to approximately 16.9 months.

The assumptions for median PFS and median OS in the control arm used for sample size calculation are derived from the Phase II studies CodeBreak 100 (median PFS: 6.8 months, median OS: 12.5 months; Skoulidis et al. 2021) and KRYSTAL-1 (median PFS: 6.5 months, median OS: 12.6 months; Jänne et al. 2022). In a conservative approach, given that CodeBreak 100 and KRYSTAL-1 are single arm Phase II studies, median PFS and median OS for the shared control arm are assumed to be slightly higher than results observed for the individual drugs (sotorasib and adagrasib).

9.2 ANALYSIS SETS

The analysis sets for the purposes of analyses are defined in Table 4.

Table 4 Analysis Sets

Analysis Set	Description
Full analysis set	All randomized participants; participants will be included in the analyses according to the treatment to which they were assigned.
Safety analysis set	All participants exposed to study treatment; participants will be analyzed according to the treatment that they actually received.
Response-evaluable set	All participants in the full analysis set with measurable disease at baseline; participants will be included in the analyses according to the treatment to which they were assigned.
PK-evaluable set	All participants who received at least one dose of study drug and had at least one post-baseline quantifiable PK sample available; participants will be analyzed according to the treatment that they actually received.

PK = pharmacokinetic.

9.3 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. The analyses specified in the Statistical Analysis Plan supersede those specified here.

9.3.1 General Considerations

The efficacy analyses will be performed in the full analysis set, unless otherwise stated, with participants grouped according to the treatment arm to which they were assigned.

Safety and tolerability analyses will be performed on the safety analysis set, with participants grouped according to the treatment that they actually received.

9.3.2 Estimation Methods for the Primary Estimand

The attributes describing the estimand related to the primary analysis are summarized in Section 3.1. The primary efficacy endpoint is PFS, as determined by the investigator.

Data for participants without the occurrence of disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

For both intercurrent events, a treatment policy strategy will be applied, i.e., PFS will be assessed irrespective of whether a participant discontinued early from study drug or started non-protocol anticancer therapy prior to disease progression. Tumor assessments will be performed as per the schedule of assessments until disease progression or death, irrespective of the occurrence of any of the intercurrent events. The investigators will be instructed accordingly.

The primary comparison of interest is the stratified log-rank test (two-sided at 5% significance level) for PFS. The stratification factors are the randomization factors as recorded in IxRS. Results from an unstratified log-rank test will also be presented. The hazard ratio for PFS will be estimated using a stratified Cox regression model in order to provide an estimate of the treatment effect. A 95% confidence interval for the hazard ratio will be provided.

The Kaplan-Meier method will be used to estimate the median PFS for each arm with 95% confidence limits, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment arms. The Brookmeyer-Crowley method will be used to construct the 95% confidence interval for the median PFS (Brookmeyer and Crowley 1982).

The impact of missing scheduled tumor assessments on PFS will be assessed by performing a sensitivity analysis based on the interval censoring analysis methods. Additional sensitivity analyses may be added and more details for sensitivity analyses will be provided in the Statistical Analysis Plan.

9.3.3 Estimation Methods for the Secondary Estimands/Endpoints

9.3.3.1 Analysis of the Key Secondary Endpoint

The attributes describing the estimands related to the key secondary objectives are summarized in Section 3.2. The key secondary efficacy endpoints are OS and TTCD.

For the analysis of OS, data for participants who are not reported as having died as of the clinical data cutoff date will be censored at the date when they were last known to be

alive (or at the time of randomization plus 1 day if no survival follow-up is available after the baseline visit).

For both intercurrent events, a treatment policy strategy will be applied, i.e., OS will be assessed irrespective of whether a participant discontinued early from study drug or started non-protocol anticancer therapy.

Estimation methods will be performed as described for the primary estimand (see Section 9.3.2). The primary comparison of interest is the stratified log-rank test (two-sided 5% significance level) for OS. Critical values at the interim and the final analyses are provided in Section 9.4.

TTCD will be assessed irrespective of whether a participant discontinued early from study drug (i.e., treatment policy strategy), and as if no non-protocol anticancer therapy is started prior to a confirmed clinically meaningful deterioration (i.e., hypothetical strategy). A while-alive strategy will be applied for participants who die before reporting any clinically meaningful deterioration. Consequently, the collection of QoL assessments will be continued until clinically meaningful deterioration, start of non-protocol anticancer therapy or death, whichever is earlier, irrespective of study drug discontinuation. The investigators will be instructed accordingly.

For the analysis of TTCD, participants without confirmed clinically meaningful deterioration as of the clinical data cutoff date (including participants who die without reported clinically meaningful deterioration) will be censored at the time of the last assessment (or at the time of randomization plus 1 day if no assessment was performed after the baseline visit). Participants who start non-protocol specified anticancer therapy will be censored at the time of the last assessment before starting the non-protocol specified anticancer therapy.

Estimation methods will be performed as described for the primary estimand (see Section 9.3.2). The primary comparison of interest for TTCD is the stratified log-rank test (two-sided 5% significance level). TTCD will be analyzed at the time when OS analysis shows statistical significance.

Sensitivity analyses for OS and TTCD will be described in the Statistical Analysis Plan.

9.3.3.2 Other Secondary Endpoints

Objective Response Rate (ORR) is defined as the proportion of participants with a complete response or PR, as assessed by the investigator according to RECIST v1.1. Participants not meeting this criterion (including participants without a post-baseline tumor assessment) will be considered non-responders.

The ORR will be compared among treatment arms using the stratified Cochran-Mantel-Haenszel test, stratified by the same factors used in the primary PFS analysis.

Confidence intervals for the difference in ORRs between the treatment arms will be determined using the normal approximation to the binomial distribution.

Duration of Response (DOR) is defined as the time from the first occurrence of a documented objective response until the first date that progressive disease or death is documented, whichever occurs first. Disease progression will be determined by the investigator according to RECIST v1.1. DOR will be assessed in participants who had an objective response during the study as determined by the investigator. Participants who have not progressed and who have not died as of the clinical data cutoff date for analysis will be censored at the time of the last tumor assessment (or at the date of first objective response plus 1 day if no tumor assessment was performed after the objective response).

The DOR analysis will be performed on the basis of a non-randomized subset of participants (specifically, participants who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. DOR will be estimated using Kaplan-Meier methodology. Comparisons between treatment arms will be made for descriptive purposes only.

For endpoints collected using EORTC QLQ-C30 and QLQ-LC13 mean scores and changes from baseline will be analyzed descriptively for each timepoint, with baseline defined as the last assessment prior to start of study treatment. TTCD analyses for scales that are not considered key secondary endpoints will be performed as described for TTCD key secondary endpoints in section 9.3.3.1.

9.3.3.3 Safety and Tolerability Analyses

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, etc.) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where

appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

PRO-CTCAE analyses will be primarily descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities during the study. PRO-CTCAE data will be analyzed at the item level.

PRO-CTCAE data will be summarized over time. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data. The number and percentage of participants reporting each symptom and the change from baseline by category (frequency of occurrence, severity, and interference) will be summarized at each assessment timepoint by treatment arm. For items that are rated on a 5-point Likert scale, the maximum post-baseline score and change from baseline will be summarized by treatment arm.

Graphical representation of PRO-CTCAE data over time will also be provided.

The analyses of the EORTC IL46 item will be descriptive, with a focus on characterizing the pattern of being troubled by side effects from treatment over the course of the study. The number and percentage of participants reporting each response option ("Not at all" to "Very much") to the item and the change from baseline by response option will be summarized at each assessment timepoint by treatment arm. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data.

9.3.4 Exploratory Analyses

The probability of CNS progression, non-CNS progression, and death will each be estimated using cumulative incidence functions. CNS progression will be defined as progression due to newly developed CNS lesions and/or progression of previously treated CNS lesions. Estimates of the CNS progression rates at 6 and 12 months with 95% confidence intervals determined on the basis of cumulative incidence functions will be presented.

Time to CNS progression as determined by the investigator according to RECIST v1.1, is defined as the time from randomization until first radiographic evidence of CNS progression. To account for the competing risks inherent in such an analysis, hazard ratios will be computed on the basis of cause-specific hazard functions.

Intracranial PFS will be estimated using Kaplan-Meier methodology.

Exploratory biomarker analyses will be performed in an effort to understand the association of biomarkers with study drug response, including but not limited to efficacy and/or adverse events, as well as emergence of resistance. Additional

pharmacodynamics analyses will be conducted as appropriate. Exploratory biomarker analyses will include assessments of biomarkers in both tumor tissue and blood. Such assessments will include but will not be limited to mutational analysis using NGS and gene expression and may also include other methods that may become available in the future.

Health utility data from the EuroQol EQ-5D-5L will be evaluated in pharmacoeconomic models. Results from health economic data analyses will be reported separately from the Clinical Study Report.

9.3.5 Other Analyses

9.3.5.1 Summaries of Conduct of Study

Enrollment, study drug administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study drug discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.3.5.2 Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, race/ethnicity, baseline disease characteristics, ECOG Performance Status, and number of prior cancer treatments) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.3.5.3 Pharmacokinetic Analyses

Individual plasma concentrations of divarasib will be listed and summarized. Divarasib PK data may be pooled and analyzed using the population PK analysis approach, as appropriate, and reported separately from the study report.

Individual plasma concentrations of sotorasib and adagrasib may be listed and summarized. Additional PK analyses (e.g., ex vivo unbound plasma concentration analysis for divarasib, sotorasib, adagrasib) may be conducted as appropriate.

9.4 INTERIM ANALYSIS

One interim analysis on OS will be performed at the time of the primary PFS analysis. The Lan-DeMets alpha spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994).

The expected number of OS events at the time of the interim analysis is approximately 153 (i.e., 66% information fraction), leading to a stopping boundary in terms of p-value $\leq$ 0.0116 at the interim analysis. Under these assumptions, the critical value for the final OS analysis will be a p-value of 0.0464.

Critical values at the interim and the final analyses will be adjusted according to the actual number of observed OS events per stage to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

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

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice
- Applicable laws and regulations.

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

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

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 250 sites globally will participate to enroll approximately 320 participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An independent Data Monitoring Committee will be employed to monitor and evaluate participant safety throughout the study. An independent review facility will collect, store, and potentially review imaging data.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data and data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

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

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

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

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

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

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

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells) • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine (serum), total protein, albumin (serum), phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and lactate dehydrogenase • Lipase • Coagulation: INR and aPTT • HIV serology: HIV-1/2 antibody • HBV serology: HbsAg, HbsAb, and total HbcAb for all individuals; HBV DNA for individuals with negative HbsAg and HbsAb tests and a positive total HbcAb test • HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test • Pregnancy test All female participants of childbearing potential will have a serum pregnancy test performed at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, nitrites, leukocyte esterase, and blood)

HbcAb = hepatitis B core antibody; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus.

Investigators must document their review of each laboratory safety report.

Appendix 3
Safety Parameters: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

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

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the electronic Caser Report Form (eCRF).

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator should report in the eCRF any postmortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS, MEDICAL DEVICE ADVERSE EVENTS, AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) and serious adverse events considered related to the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures) should be reported immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) using the Screening Adverse Event eCRF or using the paper Clinical Trial Adverse Event/Special Situations Form if the EDC is not available.

In addition, during this period, non-serious adverse events considered related to the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies) should be reported within 5 days after the investigator becomes aware of the event using the Screening Adverse Event eCRF or the paper Investigational Medical Device Adverse Event and Device Deficiency Form if the EDC system is not available.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events, adverse events of special interest, and non-serious medical device adverse events that are considered related will be reported until 28 days after the final dose of study treatment. For serious adverse events and adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF. For non-serious medical device adverse events that are considered related the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies), investigators should record all case details within 5 days on the Adverse Event eCRF. Reports will be submitted via the electronic data capture (EDC) system and will be sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form (all serious adverse events) or Investigational Medical Device Adverse Event and Device Deficiency Form (non-serious investigational medical device related), using the fax number or email

address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting events that occur more than 28 after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 after the final dose of study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment or the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures), the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event /Special Situations Form (study drug related events) or Investigational Medical Device Adverse Event and Device Deficiency Form (medical device related), using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.2 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately

(i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.4 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.5 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.6 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.7 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1) that are attributed by the investigator solely to progression of non–small cell lung cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.8 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.9 LACK OF EFFICACY OR WORSENING OF NON–SMALL CELL LUNG CANCER

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of non–small cell lung cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of non–small cell lung cancer"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on Response Evaluation Criteria in Solid Tumors, Version 1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A3–7.10 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.11 PARTICIPANT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from PRO-CTCAE or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile participant reports of treatment-related symptoms (via PRO-CTCAE) with investigator reports of adverse events. Sites are not expected to review the PRO-CTCAE or other PRO data for adverse events.

A3–7.12 SAFETY BIOMARKER DATA

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

A3–8 SPECIAL SITUATIONS(OVERDOSE, MEDICATION ERROR, DRUG ABUSE, AND/OR DRUG MISUSE)

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse} (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

    In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

After initiation of study drug, special situations associated with divarasib, sotorasib, and adagrasib and any associated adverse events will be reported until 28 after the final dose of study drug.

Special situations, regardless of whether they result in an adverse event, should be reported on the Special Situations eCRF. If there are any associated adverse events, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated adverse events should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section A3–5.

A3–9 MEDICAL DEVICE ADVERSE EVENTS

This study will comply with International Standard (ISO) 20916 on in vitro diagnostic medical devices—clinical performance studies using specimens from human subjects—good study practice and Regulation (EU) 2017/746 on in vitro diagnostic medical devices requirements for medical device adverse event collection and reporting for events associated with the use of the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures) (see also Sections 8.3.1, 8.3.2, A3–5, and A3–6).

A3–9.1 DEFINITION OF IVD MEDICAL DEVICE ADVERSE EVENT

Any untoward medical occurrence, inappropriate patient management decision, unintended disease or injury, or untoward clinical signs in subjects, users, or other persons, with any connection to study related activities, whether or not related to the IVD medical device under investigation. Adverse events can be caused by, for instance, insufficient or inadequate instructions for use, deployment, installation, operation, or any malfunction of the IVD medical device under investigation. This definition includes the malfunction or deterioration of a device which has not yet caused death or serious injury, but which could lead to death or serious injury. This definition is not intended to be used in determining whether an event is reportable to a regulatory authority. For users or other persons, this definition is restricted to events related (defined as possible, probable, or causal relationship) with the investigational IVD medical device or device-related procedures. False negative or false positive results are not considered an adverse event unless in an interventional study, inappropriate patient management decisions are made based on those false results.

A3–9.2 DEFINITION OF DEVICE DEFICIENCY

A device deficiency is any inadequacy in the identity, quality, durability, reliability, usability, safety, or performance of an investigational medical device, including malfunction of the device, use error, or inadequate manufacturer-supplied instructions (including labeling) for use, deployment, installation, or operation of the device (see Section 8.3.2).

A3–9.3 ASSESSMENT OF CAUSALITY OF MEDICAL DEVICE ADVERSE EVENTS

The circumstances surrounding the event, an evaluation of any potential alternative causes, and any knowledge about the clinical study participant, user, or other person should be used to determine whether an adverse event is considered to be related to the use of the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures). The guidance provided below should be used to assess the causality of these adverse events.

Relationship	Criteria for Classification
Not related	The relationship of the event to the device or device-related procedures can be excluded when • The event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device; the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • The serious adverse event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • The event does not depend on a false result given by the investigational device used for diagnosis, when applicable. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Relationship	Criteria for Classification
Causal	The adverse event/serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when • The event is a known side effect of the specimen collection procedures for the investigational IVD; • The event has a temporal relationship with investigational device use/application or procedures; • The serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); • Other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • Harm to the subject is due to error in use; • The event depends on a false result given by the investigational device used for diagnosis, when applicable. In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Note: Events associated with a procedure that would have been performed in a clinical study participant with or without use of the device should be classified as not related.

A3–9.4 REPORTING MEDICAL DEVICE ADVERSE EVENTS

See Section A3–5 for details on reporting medical device adverse events in participants. User injury adverse events must be reported using the paper Investigational Medical Device Adverse Event and Device Deficiency Form.

Appendix 4
Safety Plan: Management of Identified and Potential Risks

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A4–1 RISKS ASSOCIATED WITH DIVARASIB

Divarasib is not approved by health authorities, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with divarasib in completed and ongoing studies. The anticipated important safety risks for divarasib are outlined below. Please refer to the current Divarasib Investigator's Brochure for a complete summary of safety information.

A4–1.1 POTENTIAL GASTROINTESTINAL TOXICITIES (DIARRHEA, NAUSEA, VOMITING)

In 4-week toxicology studies in cynomolgus monkeys with divarasib, clinical signs of gastrointestinal intolerance with retching and vomiting were observed. Diarrhea, nausea, and vomiting have been reported in patients treated with divarasib. Please refer to the Divarasib Investigator's Brochure for additional information.

Gastrointestinal (GI) toxicities (e.g., diarrhea, nausea, vomiting) have been reported in association with the oral KRAS G12C inhibitors sotorasib (AMG 510) and adagrasib (MRTX849) (Jänne et al. 2020; Skoulidis et al. 2021).

The mechanism of action underlying GI toxicities reported with oral KRAS G12C inhibitors remains unknown. Patients should be closely monitored for signs and symptoms related to gastrointestinal effects.

Development of abdominal pain, nausea, vomiting, and clinically significant changes in stool (e.g., diarrhea, bloody stools) may necessitate more frequent monitoring, and study drug may be held if symptoms are prohibitive for normal function. Clinical evaluation for infectious (e.g., *Clostridium difficile*, enteric bacteria, and cytomegalovirus) or inflammatory (e.g., inflammatory colitis) etiologies for diarrhea should be conducted with additional consideration for gastrointestinal consultation as needed. Participants should be made aware of the risk for diarrhea, nausea, and vomiting and should be instructed to inform their treating physician and to initiate anti-emetic or anti-diarrheal medications as soon as possible if they experience these events. Participants should be treated and managed per standard of care and per protocol guidelines (see A4–4.3.1), including early or prophylactic use of anti-emetics, early use of anti-diarrheals, probiotics, and appropriate supportive care including hydration and dietary modification if clinically indicated. Participants should be reassessed within 24 hours of new or worsened symptoms, or initiation or change in supportive care measures, to ensure adequate improvement.

A4–1.2 POTENTIAL ORAL MUCOSAL IRRITATION

In nonclinical studies in mice with divarasib, microscopic evidence of laryngeal necrosis and inflammation was observed. The laryngeal findings were attributable to incidental

exposure to the higher concentration drug formulation during the gavage process leading to chemical irritation. Refer to the Divarasib Investigator's Brochure for a detailed description of the nonclinical toxicology findings.

Stomatitis and esophagitis events have been reported very uncommonly for divarasib in the clinical setting.

Participants should be instructed on proper pill swallowing without chewing or crushing the tablet. A minimum of 240 mL (8 ounces) of water should be taken with divarasib. Participants should be monitored for signs of stomatitis or mucositis.

A4–1.3 POTENTIAL ELEVATION OF HEPATIC TRANSAMINASES

In cynomolgus monkeys, minimal to mild transaminase elevation has been observed after administration of divarasib.

Hepatic transaminase elevation has been reported for the oral KRAS G12C inhibitors currently in clinical development. Treatment-related hepatic transaminase elevations (including Grade ≥3 events) have been reported with sotorasib and adagrasib in clinical trials (Jänne et al. 2020; Skoulidis et al. 2021). An association between recent PD-(L)1 inhibitor exposure and sotorasib-related hepatic transaminase elevation has been reported (Begum et al. 2021; Chour et al. 2023; Rakshit et al. 2022). In contrast, no causal association with PD-(L)1 inhibitor exposure and adagrasib-related hepatitis has been reported yet. Concurrent or lead-in sotorasib and PD(L)1 combination reported a higher incidence of Grade 3–4 treatment-related hepatotoxicity than observed with single-agent sotorasib (Li et al. 2022). Similar associations have not yet been reported with adagrasib. Results reported for adagrasib in combination with pembrolizumab have used a lower dose of adagrasib than reported for single-agent adagrasib (Jänne et al. 2022).

The mechanism underlying hepatotoxicity remains unknown. Participants will be monitored routinely with chemistry panels that include liver function tests and for signs or symptoms of hepatic pathology (e.g., jaundice, coagulopathy, abdominal pain).

Participants with underlying active liver disease (see Section 5.2) will be excluded from this study. Participants experiencing hepatic enzyme elevation should be treated and managed per standard of care and protocol guidelines (see Section A4–4.3.1).

A4–1.4 POTENTIAL DRUG INTERACTIONS

Divarasib has been shown to have the potential to induce the messenger RNA (mRNA), but not the protein levels of CYP3A4 in human hepatocyte culture. Therefore, interaction with co-administered CYP3A4 substrates cannot be excluded at this point. As such, care should be taken with co-administered drugs that are metabolized by these

enzyme systems, especially if those drugs have a narrow therapeutic index, because their systemic concentrations could be altered when co-administered with divarasib. CYP3A4 may play a role in the metabolism of divarasib, so there is a potential for drug-drug interaction with co-administered CYP3A4 modulators. Thus, caution should be taken with any medication that is metabolized by or strongly inhibits or induces this enzyme (see Section 6.8.2.1).

Divarasib has been shown to inhibit P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters in vitro. While exposure of prototypical substrates of P-gp and BCRP transporters is not predicted to be affected based on physiologically based pharmacokinetic modeling-based simulations in the clinical dose range of divarasib, interaction with co-administered P-gp, and BCRP substrates cannot be excluded. Caution should be taken with any medication that is an exclusive substrate of P-gp or BCRP with a narrow therapeutic index (see Section 6.8.2.1).

A4–2 RISKS ASSOCIATED WITH SOTORASIB

Sotorasib has been associated with hepatotoxicity and interstitial lung disease (ILD)/pneumonitis.

Hepatotoxicity

Sotorasib can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. Sotorasib has been associated with transient elevations of serum transaminases (ALT and AST). These elevations improved or resolved with dose modification or permanent discontinuation of treatment and did not result in any cases of liver failure or fatal cases in clinical studies. Cases of liver enzyme increase can be asymptomatic. Participants should be monitored for liver function (ALT, AST and total bilirubin) prior to the start of sotorasib, and during treatment with sotorasib, with more frequent testing in participants who develop transaminase and/or bilirubin elevations.

Interstitial Lung Disease (ILD)/pneumonitis

ILD/pneumonitis occurred in patients treated with sotorasib with prior exposure to immunotherapy or radiotherapy and the events can be fatal. Monitor participants for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever).

For more details on the safety profile of sotorasib, refer to the applicable local prescribing information.

A4–3 RISKS ASSOCIATED WITH ADAGRASIB

Adagrasib has been associated with gastrointestinal adverse reactions, QTc interval prolongation, hepatotoxicity, and ILD/pneumonitis.

Gastrointestinal Adverse Reactions

Adagrasib can cause severe gastrointestinal adverse reactions. Monitor and manage participants using supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated.

QTc Interval Prolongation

Adagrasib can cause QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (e.g., torsades de pointes) or sudden death. Adagrasib causes concentration dependent increases in the QTc interval (see Section 6.8.2.3)

Hepatotoxicity

Adagrasib can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. Monitor liver laboratory tests (AST, ALT, alkaline phosphatase and total bilirubin) prior to the start of and during treatment with adagrasib or as clinically indicated, with more frequent testing in participants who develop transaminase elevations.

ILD /Pneumonitis

Adagrasib can cause ILD/pneumonitis, which can be fatal. Monitor participants for new or worsening respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever) during treatment with adagrasib. Withhold adagrasib in participants with suspected ILD/pneumonitis.

For more details on the safety profile of adagrasib, refer to the applicable local prescribing information.

A4–4 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A4–4.1 DOSE MODIFICATIONS

The divarasib dose modification instructions provided are intended to serve as recommended guidelines to allow ongoing treatment for participants experiencing clinical benefit without signs or symptoms of progression while monitoring participant safety. These guidelines are intended to inform rather than supersede clinical judgment and the investigator's assessment of the benefit-risk balance in managing individual cases.

The dose of divarasib can be reduced by one dose level up to two times for management of treatment-related toxicities (i.e., from 400 mg to 200 mg and then from 200 mg to 100 mg). If further dose reduction is indicated after two dose reductions, the participant must discontinue divarasib. The Medical Monitor is available to advise as needed.

Please refer to respective local prescribing information for dose modification guidelines of sotorasib and adagrasib.

A4–4.2 TREATMENT INTERRUPTION

If divarasib has been withheld for >1 cycle because of toxicity, treatment with divarasib should be discontinued unless the investigator deems resumption of treatment to be in the best interest of the participant based on a benefit-risk assessment. Divarasib treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit-risk by the investigator and documented by the investigator. The Medical Monitor is available to advise as needed.

Please refer to respective local prescribing information for dose interruption guidelines of sotorasib and adagrasib.

A4–4.3 MANAGEMENT GUIDELINES

A4–4.3.1 Management Guidelines for Adverse Events Associated with Divarasib

Guidelines for management of specific adverse events with divarasib are outlined in Table A4-1.

Table A4-1 Guidelines for Management of Adverse Events for Participants Receiving Divarasib

Event	Action to Be Taken
Gastrointestinal Toxicities (Nausea, Vomiting)	
General	• Infectious or alternate etiology should be excluded. • Participants should be closely monitored for GI symptoms and effects on wellbeing. Participants experiencing nausea and/or vomiting should be managed according to local standards of care, including dietary modification, use of anti-emetic agents, and additional supportive care as appropriate (e.g., oral or IV hydration). • Participants should have anti-emetic medication available for use prior to initiation of divarasib (see Section 6.8.1). • Re-escalation of divarasib dose upon clinical improvement is allowed based on the investigator's assessment of benefit–risk. The Medical Monitor is available to advise as needed.
Grade 1 or 2	• Manage with supportive care according to the local standard of care. • If no response is noted with maximum first line therapy after 24–48 hours, consider initiating alternative or second line therapy. • If persistent despite maximum medical therapies, interrupt treatment with divarasib until resolution to Grade ≤ 1. Participant may resume divarasib at same dose level.

Table A4-1 Guidelines for Management of Adverse Events for Participants Receiving Divarasib

Event	Action to Be Taken
Grade ≥ 3	• Manage with supportive care according to local standard of care. • Interrupt treatment with divarasib until resolution to Grade ≤ 1. Consider resuming divarasib at one dose level lower. • Consider consultation with gastroenterologist if inadequate response despite maximum therapy and divarasib interruption. • If Grade 4, permanently discontinue divarasib.
Gastrointestinal Toxicities (Diarrhea)	
General	• Infectious or alternate etiology should be excluded. • Participants should be closely monitored for GI symptoms and effects on wellbeing. Participants experiencing diarrhea should be managed according to local standards of care, including dietary modification, use of antidiarrheal agents, and additional supportive care as appropriate (e.g., oral or IV hydration). • In participants with diarrhea and recent CPI exposure [a]: Consider early consultation with gastroenterologist in addition to assessment for infectious or inflammatory etiology (e.g., CRP, ESR, ferritin). • Dietary modifications: Stop all lactose-containing products and eat small meals. The BRAT (banana, rice, apples, toast) diet may be helpful. Encourage adequate hydration. • Participants should have anti-diarrheal medications available for use prior to initiation of divarasib (see Section 6.8.1). • Re-escalation of divarasib is allowed upon clinical improvement based on the investigator's assessment of benefit–risk. The Medical Monitor is available to advise as needed.
Grade 1 or 2	• Manage with supportive care according to the local standard of care. • If inadequate response with maximum first line therapy after 24–48 hours, consider initiating alternative or second line therapy. • If persistent despite maximum medical therapies, interrupt treatment with divarasib until resolution to Grade ≤ 1. Participant may resume divarasib at same dose level. • In participants with recent CPI exposure [a]: Consider consultation with gastroenterologist if persistent diarrhea despite maximum medical therapy.
Grade ≥ 3	• Manage with supportive care according to local standard of care. • Interrupt treatment with divarasib until resolution to Grade ≤ 1. • Consider consultation with gastroenterologist if inadequate response despite maximum therapy and divarasib interruption. • In participants with recent CPI exposure [a]: early consultation with gastroenterologist with endoscopy and biopsy is encouraged. Participants may resume divarasib at one dose level lower when diarrhea improves to Grade ≤ 1. • If Grade 4, permanently discontinue divarasib.

Table A4-1 Guidelines for Management of Adverse Events for Participants Receiving Divarasib

Event	Action to Be Taken
Elevation of Hepatic Transaminases	
General	• Participants presenting with jaundice, coagulopathy, abdominal pain or other symptoms suggestive of hepatic pathology should have liver function tests checked and imaging of the liver performed. If liver enzymes are elevated with no obvious malignant cause, a hepatologist should be consulted. • Participants experiencing hepatic enzyme elevation should be treated and managed according to local standard of care. • In participants with recent CPI exposure [a]: consider early consultation with a hepatologist and corticosteroid [b] treatment after ruling out infectious or alternative etiology.
Grade 1 or 2	• Consider more frequent monitoring until Grade ≤ 1. • In participants with recent CPI exposure [a]: consider consultation with hepatologist and oral corticosteroid [b] treatment after ruling out infectious or alternative etiology.
Grade ≥ 3	• Interrupt treatment with divarasib until resolution to Grade ≤ 1. Consider resuming divarasib at one dose level lower. • In participants with recent CPI exposure [a]: consultation with a hepatologist is encouraged. Corticosteroid [b] treatment with slow taper after ruling out infectious or alternative etiology. • If Grade 4 or any case meeting Hy's Law criteria, permanently discontinue divarasib.
Stomatitis/Mucosal Inflammation	
General	• For any grade stomatitis/mucosal inflammation, aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetics, antihistamine, corticosteroid, antacid, antifungal, and/or antibiotics) may be implemented to help manage symptoms. Diet should be modified (e.g., avoidance of spicy food) and harsh mouth washes (e.g., Listerine) should be avoided.
Grade 1	• Monitor symptoms and initiate management (see above). Re-evaluate within 48–72 hours.
Grade 2	• Interrupt divarasib and manage until Grade ≤ 1. • When stomatitis/oral mucositis improves to Grade ≤ 1, resume dosing at the same dose or one dose level lower per investigator evaluation. • For recurrent Grade 2 stomatitis or oral mucositis within 30 days, resume dosing at one dose level lower.

Table A4-1 Guidelines for Management of Adverse Events for Participants Receiving Divarasib

Event	Action to Be Taken
Stomatitis/Mucosal Inflammation (cont.)	
Grade ≥ 3	• Interrupt divarasib and manage until Grade ≤ 1. – When stomatitis/oral mucositis improves to Grade ≤ 1, resume dosing one dose level lower per investigator evaluation. • If Grade 4, permanently discontinue divarasib.

C1D1 = Cycle 1, Day 1; CPI = checkpoint inhibitor; GI = gastrointestinal.

[a] Defined as the last administered dose of CPI < 3 half-lives from C1D1 of divarasib.

[b] For Grade 1 or 2 toxicities, consider prednisone 10–20 mg QD or equivalent dose of alternative corticosteroid. For Grade 3 toxicities, consider prednisone 60 mg QD or 1 mg/kg or equivalent dose of alternative corticosteroid as deemed clinically appropriate by the investigator.

A4–4.3.2 Management Guidelines for Adverse Events Associated with Sotorasib or Adagrasib

Refer to the local sotorasib or adagrasib prescribing information and institutional guidelines for details on management of adverse events associated with sotorasib or adagrasib.

A4–4.4 MANAGEMENT OF INCREASES IN QT INTERVAL

Divarasib should be discontinued in participants who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements > 30 minutes apart) QT interval corrected through use of Fridericia's formula (QTcF) that is > 500 ms and > 60 ms longer than the baseline value
- Sustained absolute QTcF that is > 515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of participants with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such participants.

In rare circumstances, it may be acceptable to resume divarasib, at a lower dose, provided any ECG abnormalities have resolved and the participant is appropriately monitored. Clinical judgment should be applied.

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Appendix 5
Collection of Pregnancy Information

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A5–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 7 days after the final dose of sotorasib, or 6 months after the final dose of divarasib or adagrasib. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Sharing of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A5–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 4 months after the final dose of divarasib. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Sharing of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with

additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Sharing of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A5–3 ABORTIONS

A spontaneous abortion in a female participant exposed to study treatment or the female partner of a male participant exposed to divarasib should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A5–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to divarasib should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 6
Clinical Outcome Assessment Instruments

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A6–1 CLINICAL OUTCOME ASSESSMENT INSTRUMENTS

PRO instruments will be self-administered or interviewer-administered at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3). PRO instruments may be completed at home during the follow-up period as needed (see schedule of activities in Section 1.3). At the clinic, instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment. In scenarios where the non-PRO assessments (e.g., blood draws, imaging scans) are completed at a different location than the one providing treatment or are performed on a different day than study treatment administration, the non-PRO assessments can be completed before the completion of PRO questionnaires as long as the results have not been discussed with participants.

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

Participants should be given the following instructions for completing PRO instruments at home:

- Participants should complete the instruments in a quiet area with minimal distractions and disruptions.
- Participants should answer questions to the best of their ability; there are no right or wrong answers.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During clinic visits, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be 24 minutes at each specified visit during the study treatment period and 15 minutes at each specified visit during the follow-up period.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.

- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

A6–1.1 EORTC QLQ-C30

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Specimen

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Specimen

A6–1.2 EORTC QLQ-LC13

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ENGLISH



EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

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A6–1.3 NCI PRO-CTCAE

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NCI PRO-CTCAE ™ ITEMS
Item Library Version 1.0
English
Form Created on 01 December 2021

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
2b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

SPECIMEN

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

6a. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
6b. In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

7a. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7b. In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8a. In the last 7 days, did you have any RASH?	
O Yes	O No

9a. In the last 7 days, what was the SEVERITY of your ACNE OR PIMPLES ON THE FACE OR CHEST at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

10a. In the last 7 days, did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

11a. In the last 7 days, how OFTEN did you have a HEADACHE?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
11b. In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
11c. In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

12a. In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
12b. In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
12c. In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

SPECIMEN

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A6–1.4 EORTC IL46

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ENGLISH

EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

SPECIMEN

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A6–1.5 EUROQOL EQ-5D-5L

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Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g., work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

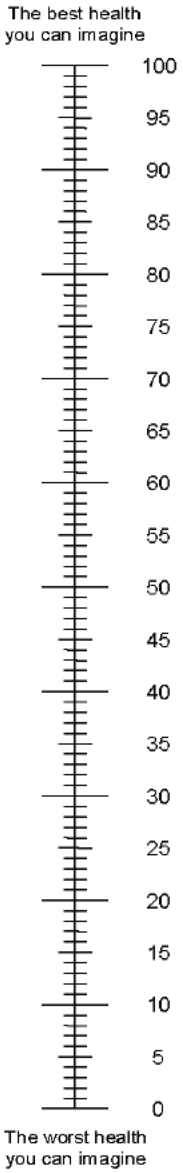
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



USA (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Appendix 7
Genetics: Use and Analysis of DNA for Mandatory Samples

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to divarasib and non-small cell lung cancer (NSCLC) and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to divarasib and treatments of this drug class and NSCLC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

DNA samples will be analyzed for germline and/or somatic variants. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to divarasib or study treatments of this class to understand the study disease or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

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

The samples will be retained while research on divarasib and treatments of this drug class or NSCLC continues but no longer than the period approved as per local requirements.

Appendix 8
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new

lesions on a different modality, because the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

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

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

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedules of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A8-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A8-1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all 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.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

having "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A8-1.

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

REFERENCES

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

Appendix 9
Drugs Known to Increase QT Interval

The following table is a sample list of drugs known to increase QT interval. This list is not exhaustive and the full list is provided in Woosley et al.

Aripiprazole	Flupentixol	Perphenazine
Artenimol+piperaquine	Gemifloxacin	Pilsicainide
Asenapine	Hydrocodone - ER	Pipamperone
Atomoxetine	Granisetron	Promethazine
Bedaquiline	Imipramine	Prothipendyl
Bendamustine	Isradipine	Rilpivirine
Bortezomib	Ketanserin	Risperidone
Bosutinib	Lapatinib	Romidepsin
Buprenorphine	Lenvatinib	Saquinavir
Capecitabine	Leuprolide	Sertindole
Ceritinib	Lithium	Sorafenib
Clomipramine	Melperone	Tacrolimus
Clozapine	Mifepristone	Tamoxifen
Crizotinib	Mirabegron	Telavancin
Cyamemazine (cyamepromazine)	Mirtazapine	Telithromycin
Dabrafenib	Moexipril/HCTZ	Tetrabenazine
Dasatinib	Nicardipine	Tiapride
Degarelix	Nilotinib	Tizanidine
Delamanid	Norfloxacin	Tolterodine
Desipramine	Nortriptyline	Toremifene
Dexmedetomidine	Ofloxacin	Trimipramine
Dolasetron	Osimertinib	Tropisetron
Efavirenz	Oxytocin	Vardenafil
Eribulin mesylate	Paliperidone	Vemurafenib
Ezogabine (Retigabine)	Panobinostat	Venlafaxine
Famotidine	Pasireotide	Vorinostat
Felbamate	Pazopanib	Zotepine
Fingolimod	Perflutren lipid microspheres	

REFERENCE

Woosley RL, Heise CW, Gallo T, et al. QTdrugs List [resource on the internet]. 2023 [cited 22 January 2024]. Available from: https://crediblemeds.org/healthcare-providers/clinical-overview-long-qttorsades.

Appendix 10
Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Product Name	IMP Designation	Marketing Authorization Status in EEA and United Kingdom	Used within Marketing Authorization
Divarasib	IMP (test product)	Unauthorized	Not applicable
Sotorasib	IMP (comparator)	Authorized	Yes
Adagrasib	IMP (comparator)	Authorized	Yes

EEA = European Economic Area; IMP = investigational medicinal product.

Appendix 11
Abbreviations

Abbreviation or Term	Definition
BCRP	breast cancer resistance protein
BEN	benign ethnic neutropenia
BICR	blinded independent central review
BID	twice daily
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CT	computed tomography
DDI	drug–drug interaction
DOR	duration of response
EBUS	endobronchial ultrasound
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
F1LCDx	FoundationOne® Liquid CDx assay
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GHS	global health status
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IL46	(EORTC) Item List 46
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	independent review facility
KEAP1	Kelch-like ECH-associated protein 1
KRAS G12C	Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine
KRAS G12C+	*KRAS G12C*-positive
LPLV	last participant, last visit

Appendix 11: Abbreviations

Abbreviation or Term	Definition
MN	mobile nursing
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetic
PO	orally; by mouth
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	PRO Common Terminology Criteria for Adverse Events
QD	once daily
QoL	quality of life
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
TTCD	time to confirmed deterioration
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

Signature Page for Protocol - BO45217 - DIVARASIB - v1 - Global/Core - Published
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Approval Task	[redacted] Company Signatory 16-Feb-2024 20:16:06 GMT+0000

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF DIVARASIB VERSUS SOTORASIB OR ADAGRASIB IN PATIENTS WITH PREVIOUSLY TREATED *KRAS G12C*-POSITIVE ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BO45217
TRIAL NAME:	*Krascendo 1*
VERSION NUMBER:	*3*
TEST PRODUCT:	Divarasib (RO7435846)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIERS:	IND Number: 147339 EU CT Number: 2024-510908-37-00 CIV/PS ID: PS-24-05-046895 NCT Number: NCT06497556
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4058 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	See electronic date stamp on the final page of this document.
2	25 October 2024
1	16 February 2024

PROTOCOL, VERSION 3:
RATIONALE

Protocol BO45217 Version 3 has been updated primarily to incorporate the changes from a global protocol clarification letter issued to sites, to revise a key secondary endpoint to 'confirmed objective response', and to align the safety-related updates with the most updated divarasib Investigator's Brochure.

Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- A key secondary endpoint, objective response rate, has been updated to 'confirmed objective response', defined as a complete response or partial response on two occasions ≥ 4 weeks to prevent overestimation of the observed response rate. Duration of response will also be assessed using confirmed objective response (Sections 1.1, 3.2, and 9).
- Text has been added to clarify that both total and direct bilirubin may be performed as a part of the chemistry panel at each visit; however, only total bilirubin is required if results are within normal range. If total bilirubin is out of range, then direct bilirubin must also be performed, as it is clinically indicated to further evaluate the abnormal finding (Section 1.3, Appendix 2).
- Schedule of activities has been updated to clarify that Patient-Reported Outcome (PRO) assessments are required only at Months 3 and 6 post-treatment discontinuation to align the timing of PRO collection with the study treatment dosing schedule (Section 1.3).
- Text has been updated to clarify that all screening assessments may be performed within 48 hours prior to Cycle 1 Day 1 and do not need to be repeated on Day 1 of Cycle 1 (Section 1.3).
- Language has been added to clarify biomarker collection during unscheduled visits and to specify requirements for biomarker sampling when treatment is interrupted at a given visit (Section 1.3).
- Guidance on timing of PROs was updated to clarify that PROs may be completed after dosing or other assessments, provided the participant has not received feedback from those assessments (Section 1.3, Appendix 6).
- Text has been updated to clarify that testing for known concomitant second oncogenic driver mutations is not required to determine eligibility, unless required by local authorities (Section 5.2).
- Text has been updated to recommend taking divarasib with sufficient water to aid swallowing, based on the in vitro data demonstrating that divarasib adipate salt has high aqueous solubility (see IBv7 section 1.2). The volume of water intake with divarasib tablet is not predicted to impact the extent of drug absorption (Section 6.1.1).

- Amlodipine and manidipine have been added as examples of CYP3A4 substrates with narrow therapeutic indices that should be avoided when co-administered with sotorasib in accordance with the sotorasib Summary of Product Characteristics (Section 6.8.2.2).
- The following have been removed since it is not reflective of current practices (Section 8.3.4).
- Requirement to file safety reports with the IB.
- Sponsor comparison of the frequency of event severity.
- The adverse events of special interest (AESIs) for divarasib have been updated to remove stomatitis/mucosal inflammation as it is no longer considered an AESI for divarasib (Section 8.3.8).
- The text has been updated to clarify that tumor tissue from bone is not acceptable (Section 8.7).
- The Sponsor's policy on trade secrets has been described in Section A1-10 to increase transparency (Section A1-10).
- The timeline and mechanism for collecting and reporting adverse events has been clarified in Table A3-1 to align with other sections of the protocol and to ensure consistent AE reporting (Appendix 3).
- Removed the word 'potential' from the gastrointestinal toxicities and elevation of hepatic transaminases risks associated with divarasib as these risks are now referred to as 'identified risks' as per the most updated Investigator’s Brochure (Appendix 4).
- General rules on how to manage participants who experience suspected immune-mediated adverse events with corticosteroids have been added for clarity (Appendix 4).
- The pregnancy reporting period for female partners of male participants was clarified to 5 days to align with the latest Investigator’s Brochure and other protocol sections (Appendix 5).
- Text was added to clarify that patients with only one potential target lesion in a previously irradiated area may be considered ineligible (Appendix 8).

Additional minor changes have been made to improve clarity and consistency. Appropriate updates have also been made to the appendices. Substantive new information appears in italics.

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PROTOCOL ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF DIVARASIB VERSUS SOTORASIB OR ADAGRASIB IN PATIENTS WITH PREVIOUSLY TREATED *KRAS* G12C-POSITIVE ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BO45217
TRIAL NAME:	*Krascendo 1*
VERSION NUMBER:	*3*
TEST PRODUCT:	Divarasib (RO7435846)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor to the contact provided below.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF DIVARASIB VERSUS SOTORASIB OR ADAGRASIB IN PATIENTS WITH PREVIOUSLY TREATED *KRAS G12C*-POSITIVE ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIERS:	IND Number: 147339 EU CT Number: 2024-510908-37-00 CIV/PS ID: PS-24-05-046895 NCT Number: NCT06497556

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of divarasib, a Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine (KRAS G12C) inhibitor, compared to locally approved KRAS G12C inhibitors (sotorasib or adagrasib) in patients with *KRAS G12C*-positive (KRAS G12C+) advanced or metastatic non–small cell lung cancer (NSCLC) who have been previously treated with standard of care treatments in the advanced or metastatic setting. Recently, several KRAS G12C inhibitors have been developed and studied in this patient population; however, the available data to date indicate that an unmet medical need still exists, and that more efficacious KRAS G12C inhibitors with acceptable safety profile and tolerability could improve the long-term outcome for patients.

OBJECTIVES AND ENDPOINTS

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 3.

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: Individuals with KRAS G12C + advanced or metastatic NSCLC who have received at least one prior systemic therapy • Endpoint: PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by BICR according to RECIST v1.1, or death from any cause (whichever occurs first) • Treatment: – Experimental arm: divarasib 400 mg QD – Control arm: KRAS G12C inhibitor (sotorasib 960 mg QD or adagrasib 600 mg BID), depending on investigator's choice, as applicable • Intercurrent events and handling strategies: – Early discontinuation from study treatment: treatment policy strategy – Start of non-protocol specified anticancer therapy prior to disease progression: treatment policy strategy • Population-level summary: hazard ratio for PFS

Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: As defined above for PFS • Endpoint: OS, defined as the time from randomization to death from any cause • Treatment: As defined above for PFS • Intercurrent events and handling strategies: – Early discontinuation from study treatment: treatment policy strategy – Start of non-protocol specified anticancer therapy: treatment policy strategy • Population-level summary: hazard ratio for OS
• *To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)*	• *Population: As defined above for PFS* • *Endpoint: confirmed objective response, defined as CR or PR on two occasions ≥4 weeks apart, as determined by BICR according to RECIST v1.1* • *Treatment: As defined above for PFS* • *Intercurrent events and handling strategies:* – *Early discontinuation from study treatment: composite variable strategy* – *Start of non-protocol specified anticancer therapy prior to best overall response: composite variable strategy* • *Population-level summary: difference between treatment arms in the proportion of individuals achieving confirmed objective response*
• To evaluate, from the participant's perspective, the functioning and impact of key disease-related symptoms of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: As defined above for PFS • Endpoint: TTCD on the EORTC QLQ-C30 dyspnea item and the physical functioning scale, and the cough scale of the QLQ-LC13 scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration (decrease from baseline in the functioning scale of at least 10 points or increase in the symptom scales of at least 10 points) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death. • Treatment: As defined above for PFS • Intercurrent events and handling strategies: – Early discontinuation from study treatment prior to a confirmed clinically meaningful deterioration: treatment policy strategy – Start of non-protocol specified anticancer therapy prior to a confirmed clinically meaningful deterioration: hypothetical strategy – Death that occurs before participants report any clinically meaningful deterioration: while-alive strategy • Population-level summary: hazard ratio for TTCD

• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• DOR, defined as the time from the first occurrence of a documented *confirmed* objective response to disease progression, as determined by BICR according to RECIST v1.1, or death from any cause (whichever occurs first)
• To evaluate the safety and tolerability of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 grading scale • Change from baseline in selected vital signs and ECG parameters • Change from baseline in selected clinical laboratory test results • Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne) as assessed through use of the NCI PRO-CTCAE • Change from baseline in diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne as assessed through use of the NCI PRO-CTCAE • Frequency of participants' response of the degree they are troubled with treatment symptoms, as assessed through use of the single-item EORTC Item List (IL46)
• To evaluate the quality of life of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Change from baseline in cough, chest pain, dyspnea, physical and role functioning, and GHS/QoL at each timepoint as assessed through use of the EORTC QLQ-LC13 and QLQ-C30 • TTCD on the EORTC QLQ-C30 role functioning and GHS/QoL scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration (decrease from baseline of at least 10 points) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death. • TTCD on the chest pain scale of the QLQ-LC13 scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration (increase of at least 10 points) that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death.

BICR = blinded independent central review; BID = twice daily; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; KRAS G12C = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; NCI = National Cancer Institute; NSCLC = non–small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; QD = once a day QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SOC = standard-of-care; TTCD = time to confirmed deterioration.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase III, randomized, active control, open-label study evaluating the efficacy and safety of divarasib versus KRAS G12C inhibitors, sotorasib or adagrasib, in patients with previously treated KRAS G12C+ advanced or metastatic NSCLC.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Active comparator	**Population Diagnosis or Condition:**	KRAS G12C-positive advanced or metastatic NSCLC previously treated with standard of care treatments in the advanced or metastatic setting
Interventional Model:	Parallel group	**Population Age:**	≥18 years or older
Test Product{s}:	Divarasib	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Sotorasib or adagrasib	**Study Treatment Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 320

STUDY TREATMENT

Participants in the experimental arm will self-administer divarasib at a dose of 400 mg by mouth (PO) once daily (QD) during each 21-day cycle. The dose of divarasib can be reduced up to two times for management of drug-related toxicities (i.e., from 400 mg to 200 mg and then from 200 mg to 100 mg).

Participants in the control arm will receive either sotorasib or adagrasib. Participants receiving sotorasib will self-administer sotorasib at a dose of 960 mg PO QD during each 21-day cycle. Participants receiving adagrasib will self-administer adagrasib at a dose of 600 mg PO twice a day during each 21-day cycle. Please refer to respective local prescribing information for dose modification guidelines of sotorasib and adagrasib.

DURATION OF PARTICIPATION

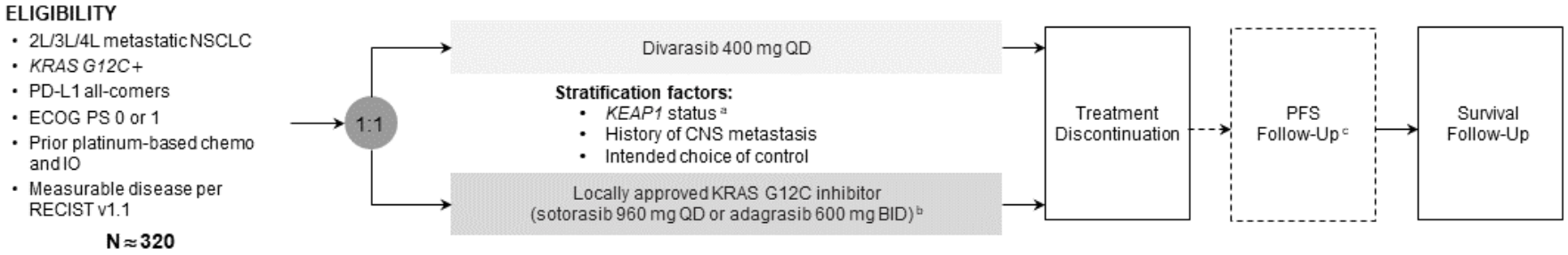
Treatment will continue until disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 or, in the case of participants continuing study treatment beyond progression, until loss of clinical benefit. The total duration of study participation for each individual is expected to range from 1 day to more than 4 years.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not applicable

1.2 STUDY SCHEMA

Figure 1 Study Design



2L = second-line treatment; 3L = third-line treatment; 4L = fourth-line treatment; BID = twice daily; chemo = chemotherapy; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; F1LCDx = FoundationOne® Liquid CDx assay; IO = immunotherapy; *KEAP1* = Kelch-like ECH-associated protein 1; *KRAS G12C* = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; *KRAS G12C* + = *KRAS G12C*-mutation positive; NSCLC = non–small cell lung cancer; PD–L1 = program cell death–ligand 1; PFS = progress-free survival; PO = orally; QD = daily; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: To ensure the control arm represents a mix of both control drug options, the Sponsor may slow or pause recruitment at sites if there is a major discrepancy in the distribution of participants receiving either control drugs.

[a] *KEAP1* mutation status will be determined either from central F1LCDx or from preexisting results from Sponsor-approved NGS tests.

[b] Depending on the local approval status, participants randomized to the control arm will receive either sotorasib 960 mg PO QD or adagrasib 600 mg PO BID; if both sotorasib and adagrasib are locally approved at a given site, investigators will choose between sotorasib and adagrasib prior to randomization, with the participant receiving the same drug throughout the duration of the treatment period (i.e., participants who receive sotorasib cannot switch to adagrasib or vice versa).

[c] Participants who discontinue study treatment for reasons other than disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will undergo PFS follow-up until radiographic disease progression, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Day(s) (Window)	Protocol Reference	Prescreening (optional) [dd]	Screening [a]		Treatment Period (21-Day Cycles)			Treatment Discontinuation [b]	Follow-Up	
					Cycles 1–2		Cycles 3 +		PFS Follow-Up	OS Follow-Up
			−28 to −15	−14 to −1	1 [c] (± 2) [d]	8 (± 2)	1 (± 3)	≤28 days after final dose of study treatment	Q6W (± 14)	~Q3M (± 14)
Informed consent [e]	8	x	x							
Review of inclusion and exclusion criteria	5.1 5.2	X	x							
Demographics	8	X	x							
Medical history and baseline conditions	8		x							
ECOG PS [f]			x		x		x	x		
EORTC QLQ-C30, EORTC QLQ-LC13 [g, h]	8.1.2 Appendix 6				x		x	x		x [i]
EuroQol EQ-5D-5L [g, h]	8.9 Appendix 6				x		x	x		x [i]
PRO-CTCAE [g, h]	8.2.6 Appendix 6				x	x	x	x		
EORTC IL46 [h, j]	8.2.6				Cycle 2 only	x	x	x		
Vital signs [h, k]	8.2.2			x	x	x	x	x		
Weight			x		x		x	x		
Height			x							

Day(s) (Window)	Protocol Reference	Prescreening (optional) [dd]	Screening [a]		Treatment Period (21-Day Cycles)			Treatment Discontinuation [b]	Follow-Up	
					Cycles 1–2		Cycles 3 +		PFS Follow-Up	OS Follow-Up
			−28 to −15	−14 to −1	1 [c] (± 2) [d]	8 (± 2)	1 (± 3)	≤28 days after final dose of study treatment	Q6W (± 14)	~Q3M (± 14)
Complete physical examination [l]	8.2.1		x		Cycle 1 only					
Limited physical examination [h, m]	8.2.1				Cycle 2 only	x	x	x		
Single 12-Lead ECG	8.2.3		x		x		x (every 3 cycles starting at Cycle 3 and as clinically indicated)	x		
Hematology [h]	Appendix 2			x	x	x	x	x		
Chemistry, *urate or uric acid, and lactate dehydrogenase (LDH)* [h, n]	Appendix 2			x	x	x	x	x		
Pregnancy test [h, o]	Appendix 2			x	x		x	x		
Urinalysis [h]	Appendix 2			x		x				
HIV, HBV, and HCV serology	Appendix 2		x							
Lipase [h]			x		x	x	x	x		
Coagulation: INR and aPTT [h]	Appendix 2			x	Cycle 1 only		x (every 3 cycles starting at Cycle 3)	x		

Day(s) (Window)	Protocol Reference	Prescreening (optional) [dd]	Screening [a]		Treatment Period (21-Day Cycles)			Treatment Discontinuation [b]	Follow-Up	
					Cycles 1–2		Cycles 3 +		PFS Follow-Up	OS Follow-Up
			−28 to −15	−14 to −1	1 [c] (± 2) [d]	8 (± 2)	1 (± 3)	≤28 days after final dose of study treatment	Q6W (± 14)	~Q3M (± 14)
Divarasib administration [p]	6.1.1				x	x	x			
Sotorasib administration [q]	6.1.2				x	x	x			
Adagrasib administration [r]	6.1.3				x	x	x			
Review of medication diary [h]	6.4				Cycle 2 only		x			
Tumor assessment [s]	8.1.1		x [t]		Every 6 weeks (± 7 days) from Day 1 of Cycle 1 for 48 weeks then every 9 weeks (± 7 days) thereafter, regardless of treatment delays until radiographic disease progression [u]			x [b]	x [v]	
Plasma PK sample [h]	8.4				Refer to Table 2					
Documentation of *KRAS G12C*-positive status [w]	8.7	x								
Archival or fresh pretreatment tumor tissue specimen for biomarkers [x]	8.7	x								
Blood sample for *KEAP1* mutation status [y]	8.7	Refer to Table 2								

Day(s) (Window)	Protocol Reference	Prescreening (optional) [dd]	Screening [a]		Treatment Period (21-Day Cycles)			Treatment Discontinuation [b]	Follow-Up	
					Cycles 1–2		Cycles 3 +		PFS Follow-Up	OS Follow-Up
			−28 to −15	−14 to −1	1 [c] (± 2) [d]	8 (± 2)	1 (± 3)	≤28 days after final dose of study treatment	Q6W (± 14)	~Q3M (± 14)
Blood sample for inherited WGS/WES analysis (at participating sites)	8.10.1				Refer to Table 2					
Blood and plasma sample for biomarkers	8.7				Refer to Table 2					
Optional: Tumor tissue sample for biomarkers [z]	8.10.2							x		
Concomitant medications [h, aa]	6.8		x		x	x	x	x		
Adverse events [h, bb]	8.3 Appendix 3		x		x	x	x	x	x	
Survival and anticancer therapy follow-up [cc]	7.1								x	x

CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organisation for Research and Treatment of Cancer; F1LCDx = FoundationOne® Liquid CDx assay; FFPE = formalin-fixed, paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; *KEAP1* = Kelch-like ECH-associated protein 1; *KRAS G12C* = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; MRI = magnetic resonance imaging; NGS = next generation sequencing; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; RBR = Research Biosample Repository; WES = whole exome sequencing; WGS = whole genome sequencing.

Notes: On study visit days, all assessments should be performed prior to dosing or initiating the next cycle of study treatment, unless otherwise specified. Refer to the cited protocol reference for activity specific details. Some assessments may be done outside the window indicated to accommodate holidays and unforeseen scheduling issues, with proper documentation in the patient medical records. The investigator should review local laboratory results prior to dosing or initiating the next cycle of study treatment; if the results are questionable, assessments should be repeated immediately. For this purpose, there is a window of ± 2 days for Cycle 2 and ± 3 days for Cycle 3 and beyond to complete the assessments, unless otherwise specified.

Unscheduled visits may be performed if clinically indicated. The following assessments should be performed at a minimum during any unscheduled visit: concomitant medications and adverse events. Additional assessments (e.g., hematology, chemistry, and ECG) may be performed as clinically indicated, per investigator discretion.

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within 28 days prior to Day 1 of Cycle 1 may be used; such assessments do not need to be repeated for screening. Screening assessments performed within 48 hours of Day 1 of Cycle 1 are not required to be repeated on Day 1 of Cycle 1. A prescreening ICF may be signed and a tumor tissue sample and blood sample may be submitted for *KRAS G12C* and/or *KEAP1* mutation assessment, respectively, before other screening procedures are initiated.

[b] Participants who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 28 days after their final dose of study drug or within 7 days after the decision of treatment discontinuation if it is out of 28 days after the last dose. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Activities required for the treatment discontinuation visit do not need to be repeated if they were performed within 7 days. Tumor assessments do not need to be repeated if one was performed within 28 days of the treatment discontinuation visit.

[c] Participants should receive their first dose of study treatment on the day of randomization if possible, and no later than 4 calendar days after randomization.

[d] The Cycle 1 Day 1 visit and procedures should be completed on the same day if possible; however, assessments or activities may be performed within 48 hours prior to the Cycle 1 Day 1 initial treatment. A window of ±2 days will be allowed for the completion of the Cycle 2 Day 1 visit.

[e] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained up to 28 days before initiation of study treatment. Prescreening is optional. Prescreening consent must be obtained before prescreening procedures are performed.

[f] ECOG PS assessment may be performed ≤96 hours before Day 1 of each cycle.

[g] Questionnaires will be self-administered or interviewer-administered (as appropriate) before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and *ideally* prior to the administration of study treatment. In scenarios where non-PRO assessments (e.g., blood draws, imaging scans) are completed at a different location than the one providing treatment or are performed on a different day *or time* than study treatment administration, the non-PRO assessments can be completed before the completion of PRO questionnaires as long as the results have not been discussed with participants. *Considering the study medication is taken orally on a daily basis, and the participant has been instructed to take the medication at approximately the same time each day, it is possible that the PROs will be completed after drug administration. This is acceptable in these situations. On days when the participant is coming to clinic, in the event participants are instructed to hold treatment until after the visit, the PROs should be completed prior to treatment administration; however, it is acceptable if they have not held treatment.* EORTC QLQ-C30, EORTC QLQ-LC13, EORTC IL46, PRO-CTCAE, and the EuroQol EQ-5D-5L questionnaires will be completed by participants on an electronic device prior to administration of study drug. For questionnaires where the translation is not available in the participant's preferred language, the participant will be exempt from completing the questionnaire until it is available. If it is determined that Day 1 of a given treatment cycle will be delayed after the participant has already completed the PRO questionnaires, the participant should not complete the Day 1 questionnaires for this cycle again. Additionally, the timing of any subsequent PRO assessments will be based on the actual Day 1 of the given cycle (e.g., if it is determined that the start of treatment at Cycle 2 will be delayed a week, the applicable Cycle 2 Day 8 PRO assessments will occur 1 week after the start of treatment, and the Day 1 of Cycle 3 assessment will occur when the next Day 1 administration of treatment is planned).

[h] Starting from Cycle 2 Day 1, for participants at participating sites who have provided written informed consent to participate in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the participant's home. Note: This is not applicable to sites in the European Economic Area *or any other region or country globally*, where mobile nursing visits are not permitted.

[i] Questionnaires will be collected 3 and 6 months after treatment discontinuation, regardless of the participant's disease progression. Questionnaires may be completed at home if there are no scheduled site visits that align with the collection timepoints (3 months and 6 months after treatment discontinuation).

[j] For Cycle 1, the EORTC IL46 questionnaire is not administered on Day 1 but on Day 8 only.

[k] Vital signs include temperature, pulse rate, respiratory rate, oxygen saturation, and systolic and diastolic blood pressure while the participant is in a seated position.

[l] A complete physical examination includes, at a minimum, assessments of the assessment of the head and neck, breast or chest wall and regional lymph nodes, and the cardiovascular, dermatologic, respiratory, gastrointestinal, and neurologic systems.

[m] A limited physical examination includes, at a minimum, symptom-directed physical examination. Investigators should pay special attention to clinical signs related to previous serious illnesses.

[n] For participants with recent checkpoint inhibitor exposure (less than 60 days prior to study treatment initiation), more frequent ad hoc liver function tests are advised if there is evidence of elevated liver enzyme or signs and symptoms suggestive of hepatitis as assessed by the investigator. *For all participants, both total and direct bilirubin may be performed as part of the chemistry panel at each visit; however, only total bilirubin is required if results are within the normal range. If total bilirubin is outside the normal range, direct bilirubin must also be performed.*

[o] For all female participants of childbearing potential: a serum pregnancy test must be performed during screening within 7 days of starting Cycle 1. At subsequent timepoints, urine pregnancy tests will be performed. A positive urine test must be confirmed by a serum test.

[p] On clinic visit days when PK samples will be collected (see Table 2), divarasib is to be administered after the PK sample collection at either the clinic or outside of the clinic to ensure the participant can take divarasib at approximately the same time each day. On Day 1 of each cycle, dispense a sufficient number of tablets to the participant to last until the next visit or, at the investigator's discretion, until the next cycle.

[q] On clinic visit days when PK samples will be collected (see Table 2), sotorasib is to be administered after the PK sample collection at either the clinic or outside of the clinic to ensure the participant can take sotorasib at approximately the same time each day. On Day 1 of each cycle, participants should receive a prescription for or be supplied with a sufficient number of tablets of sotorasib to last until the next visit or, at the investigator's discretion, until the next cycle.

[r] Adagrasib 600 mg will be administered twice daily. On clinic visit days when PK samples will be collected (see Table 2), the morning dose is to be administered at the clinic after the PK sample collection. On Day 1 of each cycle, participants should receive a prescription for or be supplied with a sufficient number of tablets of adagrsib to last until the next visit or, at the investigator's discretion, until the next cycle.

[s] Tumor assessments must be performed independently of changes to the treatment administration schedule. If a tumor assessment is performed early or late, subsequent assessments should be conducted according to the original schedule based on Day 1 of Cycle 1. All participants must undergo an MRI or CT scan (with contrast) of the brain at screening and at each subsequent tumor assessment. In the event of an equivocal CT scan, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases.

[t] All screening tumor assessments (unless otherwise specified) should be completed within 28 days prior to randomization.

[u] Participants who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments every 6 weeks (± 7 days) after initial documentation of progression or more frequently, if clinically indicated, regardless of time in study, until treatment is discontinued. Refer to Section 8.1.1 for more details.

[v] Participants who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity, symptomatic deterioration) will continue to undergo tumor assessments every 6 weeks (±7 days) until radiographic disease progression, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. In the absence of radiographic disease progression, tumor assessments should continue regardless of whether a participant starts a new anticancer therapy.

[w] For all participants enrolled based on preexisting test results, a full, legible, and de-identified report of the molecular test for *KRAS G12C* is required and must be submitted to the Sponsor's central laboratory within 30 days of randomization.

[x] For all enrolled participants, a mandatory pretreatment tumor specimen is required along with an associated pathology report for biomarker objectives. Tumor tissue samples must be collected before study treatment begins. If a participant has a preexisting test result for *KRAS G12C*, the representative tumor specimen must be confirmed available during screening and submitted to the central laboratory within 30 days of randomization. If preexisting test results are not available for KRAS G12C mutation status, a representative tumor specimen must be submitted during screening or optional prescreening for central assessment of KRAS G12C biomarker eligibility. If a participant has already submitted a pretreatment tumor specimen to centrally assess *KRAS G12C* biomarker eligibility, an additional tumor specimen is not required. Refer to Section 8.7 for specific tumor specimen requirements.

[y] For all prospective participants with *KRAS G12C*-positive tumors, a blood sample must be sent to the Sponsor's designated NGS diagnostic laboratory for determination of *KEAP1* mutation status using F1LCDx during screening or optional prescreening, even if a prospective participant has a preexisting *KEAP1* mutation test result. While central assessment of *KEAP1* mutation status is preferred for stratification, participants may use preexisting *KEAP1* results from Sponsor-approved NGS tests that are performed at an appropriately accredited/certified laboratory. If central results are available at randomization, participants will be considered to have a *KEAP1* mutation detected if either the central or pre--existing result has a *KEAP1* mutation (detecting a mutation on both tests is not required). For participants stratified on preexisting *KEAP1* test results, the full, legible, and de-identified NGS report (all pages and attachments) must be submitted to the Sponsor's central laboratory within 30 days of randomization. Sponsor-approved NGS tests for *KEAP1* status must have complete exonic coverage of *KEAP1* and report all variants.

[z] Optional tumor biopsy (FFPE tumor tissue samples) will be collected at disease progression from participants who have provided written consent and if collection of tumor biopsy is deemed clinically feasible. If tissue is not limiting, a fresh frozen tumor tissue sample (snap frozen) is also requested. If possible, optional fresh tumor biopsies should be obtained within 48 hours of the participant's final dose of study treatment, but no later than 8 weeks from progression assessment and prior to initiation of subsequent anticancer therapy. *For participants continuing treatment beyond progression, biopsies should still be obtained no later than 8 weeks after* the progression assessment. Tumor biopsy of the growing lesion is preferred. Refer to Section 8.10.2 for specific tumor specimen requirements.

[aa] Includes any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit.

[bb] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention and serious adverse events considered related to Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures) should be reported. After initiation of study treatment, all adverse events will be reported until 28 days after the final dose of study treatment or until initiation of a new anticancer therapy, whichever occurs first. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Appendix 3).

[cc] After treatment discontinuation, information on survival status and new anticancer therapy will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death (unless the participant withdraws consent, is lost to follow-up [see Section 7.3], or the Sponsor terminates the study). If a participant requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the participant withdraws from the study, the study staff may use a public information source (e.g., county records), if allowed by local laws, to obtain information about survival status only.

[dd] The prescreening visit and all procedures listed within it are optional, and can be performed based on investigators discretion, patient's status and local laws.

Table 2 Schedule of Blood-Based Pharmacokinetic and Biomarker Samples

Visit	Timepoint	Sample Type
Prescreening	Any time	Blood for *KEAP1* mutation status [a]
Screening	Days −28 to −1	
Cycle 1 Day 1	Predose	Blood for WGS/WES [b]
		Blood for NGS control
		Plasma for divarasib PK [c]
		Plasma for adagrasib or sotorasib PK [c]
		Blood for biomarkers
		Plasma for safety biomarkers
Cycle 1 Day 8	Any time	Plasma for safety biomarkers
Cycle 2 Day 1 [d]	Predose	Plasma for divarasib PK [c]
		Plasma for adagrasib or sotorasib PK [c]
	Any time	Blood for biomarkers
		Plasma for safety biomarkers
Cycle 2 Day 8 [d]	Any time	Plasma for safety biomarkers
Cycles 3-8 Day 1 [f]	Any time	Plasma for safety biomarkers
Every odd Cycles 3 + Day 1 [d]	Predose	Plasma for divarasib PK [c]
		Plasma for adagrasib or sotorasib PK [c]
	Any time	Blood for biomarkers [e]
Treatment discontinuation	Any time	Plasma for divarsib PK
		Plasma for adagrasib or sotorasib PK
		Blood for biomarkers [f]
		Plasma for safety biomarkers [f]
Unscheduled visit	As clinically indicated	Plasma for divarasib PK
		Plasma for adagrasib or sotorasib PK
		Plasma for safety biomarkers *f*
		Blood for biomarkers [e]

ADA = anti-drug antibody; F1LCDx = FoundationOne® Liquid CDx assay; *KEAP1* = Kelch-like ECH-associated protein 1; NGS = next generation sequencing; PK = pharmacokinetic; WES = Whole Exome Sequencing; WGS = Whole Genome Sequencing.

[a] For all prospective participants with *KRAS G12C*-positive tumors, a blood sample must be sent to the Sponsor's designated NGS diagnostic laboratory for determination of *KEAP1* mutation status using F1LCDx during screening or optional prescreening, even if a prospective participant has a preexisting *KEAP1* mutation test result. While central assessment of *KEAP1* mutation status is preferred for stratification, participants may use preexisting *KEAP1* results from Sponsor-approved NGS tests that are performed at an appropriately accredited/certified laboratory. If central results are available at randomization, participants will be considered to have a *KEAP1* mutation detected if either the central or preexisting result has a *KEAP1* mutation (detecting a mutation on both tests is not required). For participants stratified on preexisting *KEAP1* test results, the full, legible, and de-identified NGS report (all pages and attachments) must be submitted to the Sponsor's central laboratory within 30 days of randomization. Sponsor-approved NGS tests for *KEAP1* status must have complete exonic coverage of *KEAP1* and report all variants.

[b] Not applicable for a site that has not been granted approval for WGS/WES. Collection of samples is preferred prior to dosing on Day of Cycle 1 but can be collected at any time during the course of the study.

[c] *On the days of clinic visits for PK collection, participants on a morning regimen of daily divarasib or sotorasib should hold their morning dose. A predose plasma PK sample at the clinic should be collected within a window of 2 hours to 5 minutes prior to divarasib or sotorasib dose administered in the clinic. The exact time of divarasib or sotorasib dosing and the PK draw (clock times) should be noted by the clinic staff.*

Participants on an evening (or pm) regimen of daily divarasib or sotorasib will take their dose at home in the evening prior to the day of clinic visit for PK collection. While there is no recommended window of PK collection for pm regimen participants, the site staff should ensure that the exact date and timing of at-home divarasib or sotorasib dose from the previous evening is noted on the eCRF. The exact time of PK draw (clock time) should also be noted.

On the days of clinic visit for PK collection, participants on the twice daily regimen of adagrasib should hold their first (morning) dose. A predose plasma PK sample at the clinic should be collected within a window of 2 hour to 5 minutes prior to adagrasib dose administered in the clinic. The exact time of adagrasib dosing and the PK draw (clock times) should be noted *by the clinic staff.*

[d] For participants at participating sites who have provided written informed consent to participate in mobile nursing visits, the sample collection(s) for this visit may be performed by a trained nursing professional at the participant's home. Note: This is not applicable to sites in the European Economic Area *or any other region or country globally*, where mobile nursing visits are not permitted.

[e] Starting on Cycle 3, blood collection for biomarkers will occur on Day 1 of every odd cycle (Cycle 3, 5, 7, etc.) up to and including Cycle 17 and every 9 weeks thereafter to match tumor assessment visits. Blood collections for biomarkers can occur at any timepoint relative to dosing and are not required to be collected before study drug administration. *In a case of treatment interruption, sample collection will be resumed once the participant resumes dosing.*

[f] Blood collection for biomarkers and plasma collection for safety biomarkers will occur at treatment discontinuation or disease progression, whichever occurs first.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of divarasib, a KRAS G12C inhibitor, compared to locally approved KRAS G12C inhibitors (sotorasib or adagrasib) in patients with *KRAS G12C*-positive (KRAS G12C+) advanced or metastatic non–small cell lung cancer (NSCLC) who have been previously treated with standard of care treatments in the advanced or metastatic setting. Recently, several KRAS G12C inhibitors have been developed and studied in this patient population; however, the available data to date indicate that an unmet medical need still exists, and that more efficacious KRAS G12C inhibitors with acceptable safety profile and tolerability could improve the long-term outcome for patients.

2.2 BACKGROUND

Lung cancer is the leading cause of cancer death in the world (Sung et al. 2021). Standard first line treatment for advanced or metastatic NSCLC (including KRAS G12C +) includes platinum-based chemotherapy, immunotherapy, or a combination of chemotherapy and immunotherapy. Subsequent treatments include: platinum-based chemotherapy or immunotherapy for patients who had not previously received those therapeutic modalities, docetaxel or other non-specific chemotherapy agents, or a clinical trial (Postmus et al. 2017; National Comprehensive Cancer Network [NCCN] 2024). NSCLC that has been treated with standard of care chemotherapy and/or immunotherapy in the advanced or metastatic setting has a poor prognosis. Genomic and molecular screening for predictive biomarkers has become increasingly important for NSCLC and has transformed patient outcomes (Restrepo et al. 2023). KRAS G12C + NSCLC represents a genomically distinct subset of the disease for which targeted therapies have recently become available. Patients with KRAS G12C + NSCLC initially (e.g., first and/or second line) receive similar treatments as patients who have *KRAS G12C*-negative NSCLC in the absence of other actionable driver alterations. For patients with KRAS G12C+ NSCLC, several oral therapies specifically targeting the mutation have been developed and are available in many countries for patients who have received standard first line metastatic NSCLC treatments.

Divarasib (also known as GDC-6036) is an oral, covalent, anticancer therapeutic agent that selectively inhibits only the G12C mutant KRAS receptor. The mixed control arm in this study includes locally approved KRAS G12C inhibitors sotorasib and adagrasib (approvals vary by geographical region), both of which represent an option for patients with previously treated KRAS G12C + advanced or metastatic NSCLC. Sotorasib (AMG 510) and adagrasib (MRTX849) are small molecules that irreversibly inhibits KRAS G12C by locking it in its inactive guanosine diphosphate-bound state, similar to divarasib. Divarasib has been shown to be 5 to 20 times as potent and up to 50 times as selective in vitro as sotorasib and adagrasib (Purkey 2022). In a Phase I study,

divarasib was evaluated in patients with advanced or metastatic cancers, including 60 patients with NSCLC (Sacher et al. 2023). Among the patients with NSCLC, the confirmed response rate was 53.4% (95% CI: 39.9–66.7) and the median progression free survival (PFS) was 13.1 months (95% CI: 8.8–not evaluable), indicating promising clinical anti-tumor activity in a similar patient population to those who will be enrolled in this trial.

Detailed information on divarasib is provided in the Divarasib Investigator's Brochure. Detailed information on sotorasib and adagrasib is provided in the respective local prescribing information.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the efficacy and safety of divarasib, a selective inhibitor of KRAS G12C, to address an unmet medical need in patients with previously treated KRAS G12C + advanced or metastatic NSCLC. Divarasib will be compared to KRAS G12C inhibitors (sotorasib or adagrasib). In countries where both sotorasib and adagrasib are approved, investigators will have a choice between the two therapies.

Divarasib has been investigated as a monotherapy and in combination with other anticancer therapies at multiple dose levels across several tumor types in a Phase I study (GO42144). In the monotherapy arm of the study, divarasib was found to have promising anticancer activity in patients with KRAS G12C + solid tumors, including NSCLC, and also demonstrated an acceptable safety profile (Sacher et al. 2023). The risks of gastrointestinal toxicities (diarrhea, nausea, and vomiting), and elevation of hepatic transaminases were monitorable, manageable, and reversible.

Refer to Appendix 4 for information on anticipated risks for divarasib and risk mitigation measures, including guidelines for managing adverse events associated with divarasib.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of divarasib may be found in the Divarasib Investigator's Brochure.

Taking into account the safety and clinical activity data for divarasib in patients with KRAS G12C + NSCLC, the Sponsor has assessed the benefit–risk profile of single-agent divarasib as the experimental arm of this study (BO45217) to be acceptable.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

This study will evaluate the efficacy and safety of divarasib compared with locally approved KRAS G12C inhibitors (sotorasib or adagrasib) in participants with previously treated KRAS G12C + advanced or metastatic NSCLC.

3.1 PRIMARY OBJECTIVE AND CORRESPONDING ESTIMANDS

The primary objective for the study expressed using the estimand framework in accordance with the ICH E9(R1) statistical principles for clinical trials (ICH 2020) is described below.

Primary Objective	Estimand Definition
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: Individuals with KRAS G12C + advanced or metastatic NSCLC who have received at least one prior systemic therapy • Endpoint: PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by BICR according to RECIST v1.1, or death from any cause (whichever occurs first) • Treatment: – Experimental arm: divarasib 400 mg QD – Control arm: KRAS G12C inhibitor (sotorasib 960 mg QD or adagrasib 600 mg BID), depending on investigator's choice, as applicable • Intercurrent events and handling strategies: – Early discontinuation from study treatment: treatment policy strategy – Start of non-protocol specified anticancer therapy prior to disease progression: treatment policy strategy • Population-level summary: hazard ratio for PFS

BICR = blinded independent central review; BID = twice daily; KRAS G12C = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; NSCLC = non–small cell lung cancer; PFS = progression-free survival; QD = once a day; RECIST = Response Evaluation Criteria in Solid Tumors; SOC = standard-of-care.

3.2 SECONDARY OBJECTIVES AND CORRESPONDING ESTIMANDS AND ENDPOINTS

The key secondary objectives for the study are expressed using the estimand framework in accordance with the ICH E9(R1) statistical principles for clinical trials (ICH 2020). Other secondary objectives and corresponding endpoints are described below.

Key Secondary Objectives	Estimand Definitions
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: As defined above for PFS • Endpoint: OS, defined as the time from randomization to death from any cause • Treatment: As defined above for PFS • Intercurrent events and handling strategies: – Early discontinuation from study treatment: treatment policy strategy – Start of non-protocol specified anticancer therapy: treatment policy strategy • Population-level summary: hazard ratio for OS
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: As defined above for PFS • Endpoint: *confirmed* objective response, defined as CR or PR *on two occasions ≥4 weeks apart,* as determined by BICR according to RECIST v1.1 • Treatment: As defined above for PFS • Intercurrent events and handling strategies: – Early discontinuation from study treatment: composite variable strategy – Start of non-protocol specified anticancer therapy prior to best overall response: composite variable strategy • Population-level summary: difference between treatment arms in the proportion of individuals achieving *confirmed* objective response
• To evaluate, from the participant's perspective, the functioning and impact of key disease-related symptoms of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: As defined above for PFS • Endpoint: TTCD on the EORTC QLQ-C30 dyspnea item and the physical functioning scale, and the cough scale of the QLQ-LC13 scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death. • Treatment: As defined above for PFS • Intercurrent events and handling strategies: – Early discontinuation from study treatment prior to a confirmed clinically meaningful deterioration: treatment policy strategy – Start of non-protocol specified anticancer therapy prior to a confirmed clinically meaningful deterioration: hypothetical strategy – Death that occurs before participants report any clinically meaningful deterioration: while-alive strategy • Population-level summary: hazard ratio for TTCD

Other Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• DOR, defined as the time from the first occurrence of a documented *confirmed* objective response to disease progression, as determined by BICR according to RECIST v1.1, or death from any cause (whichever occurs first)
Other Secondary Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 grading scale • Change from baseline in selected vital signs and ECG parameters • Change from baseline in selected clinical laboratory test results • Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne) as assessed through use of the NCI PRO-CTCAE • Change from baseline in diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne as assessed through use of the NCI PRO-CTCAE • Frequency of participants' response of the degree they are troubled with treatment symptoms, as assessed through use of the single-item EORTC Item List (IL46)
• To evaluate the quality of life of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Change from baseline in cough, chest pain, dyspnea, physical and role functioning, and GHS/QoL at each timepoint as assessed through use of the EORTC QLQ-LC13 and QLQ-C30 • TTCD on the EORTC QLQ-C30 role functioning and GHS/QoL scales and the chest pain scale of the QLQ-LC13; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death.

BICR = blinded independent central review; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; KRAS G12C = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TTCD = time to confirmed deterioration.

3.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Exploratory objectives and corresponding endpoints are described below.

Exploratory Objectives	Corresponding Endpoints
• To assess the CNS activity of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Cumulative incidence rates of CNS progression as determined by BICR according to RECIST v1.1, at 6 and 12 months • Time to CNS progression as determined by BICR according to RECIST v1.1, defined as the time from randomization until first radiographic evidence of CNS progression • Intracranial PFS as determined by BICR according to RECIST v1.1, defined as the time from randomization until first radiographic evidence of CNS progression or death from any cause (whichever occurs first)
• To characterize pharmacokinetics of divarasib	• Plasma concentration of divarasib at specified timepoints
• To characterize pharmacokinetics of sotorasib	• Plasma concentration of sotorasib at specified timepoints
• To characterize pharmacokinetics of adagrasib	• Plasma concentration of adagrasib at specified timepoints
• To evaluate potential relationships between drug exposure and the efficacy and safety of divarasib	• Relationship between plasma concentration or PK parameters for divarasib and efficacy endpoints • Relationship between plasma concentration or PK parameters for divarasib and safety endpoints
• To evaluate potential relationships between selected covariates and exposure to divarasib	• Relationship between selected covariates and plasma concentration or PK parameters for divarasib

Exploratory Objectives	Corresponding Endpoints
• To identify and/or evaluate biomarkers that are predictive of response to divarasib compared with KRAS G12C inhibitors (sotorasib and adagrasib) (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to divarasib compared with KRAS G12C inhibitors, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of divarasib activity (i.e., pharmacodynamic biomarkers) compared with KRAS G12C inhibitors, or can increase the knowledge and understanding of disease biology and drug safety or pharmacokinetics	• Relationship between biomarkers in blood, plasma, and tumor tissue (listed in Section 8.7) and efficacy, safety, PK, or other biomarker endpoints
• To evaluate and compare participants' health status to generate utility scores for use in economic models for reimbursement	• Health status, as assessed by the EuroQol EQ-5D-5L questionnaire

BICR = blinded independent central review; CNS = central nervous system; KRAS G12C = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase III, randomized, active control, open-label study evaluating the efficacy and safety of divarasib versus KRAS G12C inhibitors, sotorasib or adagrasib, in patients with previously treated KRAS G12C + advanced or metastatic NSCLC.

Approximately 320 participants will be randomized in a 1:1 ratio to receive either divarasib 400 mg by mouth (PO) once daily (QD) (experimental arm) or a locally approved KRAS G12C inhibitor (control arm). Depending on the local approval status, participants randomized to the control arm will receive either sotorasib 960 mg PO QD or adagrasib 600 mg PO twice daily (BID); if both sotorasib and adagrasib are locally approved at a given site, investigators will choose between sotorasib and adagrasib prior to randomization, with the participant receiving the same drug throughout the duration of the treatment period (i.e., participants who receive sotorasib cannot switch to adagrasib

or vice versa). The aim is to provide an investigator's choice option as broadly as possible in this study according to regulatory approval status (e.g., if control drug is approved but not yet widely available locally, the Sponsor will provide the drug when possible). However, in situations where there are supply limitations and the Sponsor cannot obtain adequate supply of one of the control drugs, sites may be limited to selection of the other control drug for some period of time (i.e., until the drug becomes locally available or the Sponsor can source it to supply centrally). During these periods, investigators will still have the choice to enroll patients that they feel are suitable for the control drug available.

The proportion of participants receiving each control drug will be monitored by the Sponsor.

To ensure the control arm represents a mix of both control drug options, the Sponsor may slow or pause recruitment for one of the drugs if there is a major discrepancy in the distribution of participants receiving either control drugs.

Randomization will be stratified by *KEAP1* mutation status (mutation detected or not detected/unknown) determined by the Sponsor's designated testing laboratory or preexisting results from Sponsor-approved tests, history of CNS metastasis (yes or no), and intended KRAS G12C inhibitor in the control arm (sotorasib or adagrasib). Unknown results for *KEAP1* are not allowed for preexisting NGS tests.

Participants should receive the first dose of study treatment on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 4 calendar days after randomization. The assigned study treatment will continue until progression of disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, intolerable adverse events, withdrawal of consent, death, or Sponsor termination, whichever occurs first. Participants who discontinue study treatment prior to radiographic progression of disease according to RECIST v1.1 will continue to have tumor assessments, even if they start new anticancer therapy, according to the schedule of activities (Section 1.3) until progression of disease according to RECIST v1.1, withdrawal of consent, lost to follow-up, death, or Sponsor termination.

The primary objective will be evaluated using radiographic assessments of the tumor according to RECIST v1.1 at the frequency specified in the schedule of activities (Section 1.3).

The study includes a screening period of up to 28 days, a treatment period, and a long–term follow-up period for PFS and overall survival (OS). Participants who discontinue study treatment for reasons other than disease progression will undergo PFS follow up until documentation of progression of disease, withdrawal of consent, lost to follow-up, death, or discontinuation of the study. After confirmed disease progression, participants from the PFS follow-up will enter survival follow-up. All participants who

discontinue study treatment will be followed for OS from the safety follow-up until death, withdrawal of consent from the study, lost to follow-up, or termination of the study by the Sponsor.

In order to obtain information for eligibility and stratification for this study, *KRAS G12C* mutation testing for eligibility and/or *KEAP1*-mutation testing for stratification may be performed as prescreening ahead of the screening period. Prescreening is optional and not mandatory for study participation but may expedite screening activities. Participants will be required to sign a separate informed consent form to participate in prescreening. The prescreening testing(s) will be performed in tumor tissue for *KRAS G12C* mutations (only for participants without a preexisting result) and blood sample for *KEAP1* mutations (only for participants whose tumors are KRAS G12C + as determined by preexisting results or during this prescreening period).

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities and a sample collection schedule are provided in Section 1.3 (see Table 1 and Table 2).

Imaging data used for tumor assessments by the investigator will be collected to enable a blinded independent central review (BICR) of response endpoints. An independent review facility (IRF) will review all available (de-identified) radiographic tumor assessments to assess tumor response according to RECIST v1.1. Details of the IRF's responsibilities and procedures will be specified in a separate IRF charter.

An independent Data Monitoring Committee (iDMC) will be established to conduct periodic reviews of aggregate safety data. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the frequency of the reviews, the summary of the data, and their roles and responsibilities.

4.1.1 Treatment after Disease Progression

Participants experiencing clinical benefit in the judgment of the investigator while receiving study treatment may continue study treatment beyond disease progression (as defined by RECIST v1.1) at the investigator's discretion, if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of signs and symptoms indicative of unequivocal progression of disease (including worsening of laboratory values [e.g., new or worsening hypercalcemia])
- No decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

- Written consent from participants to acknowledge deferring alternative treatment options in favor of continuing study treatment at the time of initial progression

4.1.2 Patient Input into Study Design

Representatives from an organization within the patient community were interviewed and asked to provide feedback on the following aspects of the study:

- Study design, endpoints, inclusion and exclusion criteria activities, and patient-reported outcome (PRO) assessments
- Recruitment and retention

This feedback was taken into consideration when developing the protocol.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

This study will be conducted in patients with advanced or metastatic NSCLC that harbors a *KRAS G12C* mutation and have received prior systemic therapies for advanced or metastatic disease. *KRAS G12C* is a well-established oncogenic driver mutation and defines a distinct subgroup of NSCLC with a prevalence of approximately 12% (varies by region/race). Patients with KRAS G12C + NSCLC that have progressed after standard therapies have limited treatment options and a generally poor prognosis. Recently, specific targeted inhibitors of KRAS G12C have been developed, providing a more personalized treatment option for this NSCLC biomarker defined subset. All of the study drugs used in this study are specific inhibitors of KRAS G12C. The control drug(s) for this study has been approved for use in this patient population in the countries participating in this study.

4.2.2 Rationale for Control Arm

This is a concurrent active treatment control study evaluating the efficacy and safety of divarasib compared to locally approved therapies within the same therapeutic class of oral KRAS G12C inhibitors. The intent of this study is to demonstrate a difference between the experimental arm of the study (divarasib) and the mixed control arm of approved KRAS G12C inhibitors (sotorasib or adagrasib). The currently available nonclinical and clinical data support evaluating whether divarasib can improve on the efficacy established by therapies, with an acceptable safety and tolerability profile.

The control arm of this study includes locally approved KRAS G12C inhibitors. Sotorasib 960 mg PO QD has been approved for previously treated KRAS G12C + NSCLC in several countries across the globe. In many countries, sotorasib has become a standard-of-care treatment option given that it has demonstrated a statistically significant increase in PFS when compared to cytotoxic chemotherapy (de Langen et al. 2023). Sotorasib also represents an oral option with a favorable tolerability profile compared to the alternative of cytotoxic chemotherapy, which is administered every three weeks via intravenous infusion. Adagrasib 600 mg PO BID is also a specific

KRAS G12C inhibitor that has been approved in several countries and represents a standard-of-care option for patients previously treated with standard therapies (Jänne et al. 2022). Based on the available data published to date, sotorasib and adagrasib are considered clinically similar in regard to efficacy (sotorasib PFS: 5.6–6.8 months; adagrasib median PFS: 6.5 months) (Skoulidis et al. 2021; Jänne et al. 2022; de Langen et al. 2023), and multinational treatment guidelines recommend either as an acceptable treatment option for the disease setting in which this trial will be conducted (Hendriks et al 2023; NCCN 2024). The approval status and use of sotorasib and adagrasib also varies by country. While the drugs have the same mechanism of action and have similar clinical efficacy, they are not considered interchangeable, and physicians take a number of patient and clinical factors into consideration when choosing which KRAS G12C inhibitor to use in countries where both are approved. Therefore, in a global clinical trial aiming to enroll a representative patient population with KRAS G12C + advanced or metastatic NSCLC, it is clinically appropriate to include a mixed control arm of both of the approved in class alternatives.

4.2.3 Rationale for Open-Label Design

An open-label design was selected due to the technical and practical complexities that would be faced in blinding the IMPs. There is a significant difference in the number of tablets required each day for each IMP (refer to Table 3 for more details). Given the large variation in required number of tablets per day, combined with one of the control options being dosed twice daily (as opposed to once daily), a blinded study would involve participants taking a high number of placebo tablets per day, which could have an impact on quality of life and the patient experience on the trial. Further, while all three study drugs have similar mechanisms of action, there are important differences in the toxicity and drug interaction profiles, adverse event management, and use of concomitant medications, which are drug-specific. Blinding of treatments in this scenario would place undue burden on both participants and investigators.

In order to provide a technically feasible and patient-centric approach, with lower risk of non-compliance, medication errors, and suboptimal management of study treatment toxicities, adequate steps have been taken to ensure the validity of data in an open-label study design. This includes performing efficacy assessments at the same frequency in both arms, adhering to protocol-defined schedules, and determining the strategy for the final analysis of the primary endpoint prior to study start, including predefined methods for handling missing data and censoring rules. Well established disease assessment criteria will be used uniformly across all arms of the study (RECIST v1.1) and the primary efficacy endpoint of PFS will be assessed by blinded independent central review. The study is also powered to test for overall survival. Efficacy analyses will only be performed at the pre-specified analysis timepoints in the protocol (primary analysis once the number of PFS events presented in Section 9.1.1 have occurred in the full analysis set [see Section 9.2]). The Sponsor will not review aggregated efficacy data by treatment arm prior to release of Treatment Assignment Information data.

4.2.4 Rationale for Biomarker Assessments

NSCLC is a biologically heterogeneous disease. Therefore, all participants may not be equally likely to benefit from treatment with divarasib. Blood, plasma, and tissue samples will be assessed for predictive biomarkers in an effort to identify those participants with KRAS G12C + tumors who are most likely to respond to divarasib. In addition, pharmacodynamic biomarkers will be assessed in blood samples to demonstrate evidence of biologic activity of divarasib in participants. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

Whole genome sequencing (WGS) or whole exome sequencing (WES) of blood and tissue samples will be conducted to identify somatic variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. DNA extracted from blood or PBMCs will be compared with DNA extracted from tissue to distinguish somatic variants from germline variants. Genomics is increasingly informing researcher's understanding of disease pathobiology. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

In this study, archival or fresh NSCLC tumor tissue samples from participants without preexisting *KRAS G12C* positive test results will be submitted for *KRAS G12C* mutation status testing by a central laboratory through the use of the investigational Qiagen therascreen *KRAS* RGQ PCR assay. The Qiagen therascreen *KRAS* RGQ PCR assay is an U.S. Food and Drug Administration (FDA)-approved companion diagnostic for sotorasib, which received accelerated approval for the treatment of adult patients with KRAS G12C + advanced or metastatic NSCLC, who have received at least one prior systemic therapy. Testing may be performed during the optional prescreening or screening period to assess biomarker eligibility. If an archival tumor tissue sample is unavailable or determined to be unsuitable for the required *KRAS G12C* testing,

participants may undergo a biopsy at prescreening or screening if the investigator deems it safe and clinically feasible. When archival tumor specimens are used for *KRAS G12C* testing, there is no additional risk from a biopsy for a prospective participant with regard to use of the investigational Qiagen therascreen *KRAS* RGQ PCR assay. Prospective participants undergoing a biopsy to provide a freshly collected tumor specimen for the use of the investigational Qiagen therascreen *KRAS* RGQ PCR assay may incur additional non-serious risks from the biopsy.

Pre-treatment blood samples will also be collected from all prospective *KRAS G12C* + participants for *KEAP1* mutation status testing by a Sponsor-designated laboratory during the optional prescreening or screening period. This study may enroll individuals with *KRAS G12C* + NSCLC regardless of *KEAP1* mutation status; however, participants will be stratified by *KEAP1* status (mutation detected vs. not detected/unknown) through central use of the FDA approved Foundation Medicine FoundationOne® Liquid CDx (F1LCDx) assay or preexisting results from Sponsor-approved NGS tests that are performed at appropriately accredited/certified laboratories (unknown results for *KEAP1* are not allowed if using preexisting NGS tests). As a blood sample will be collected using minimally invasive sampling procedures, there is minimal risk to a prospective participant with regard to the use of Foundation Medicine F1LCDx assay.

4.2.5 Rationale for Stratification Factors

To ensure balance during randomization, *KEAP1* mutation status, history of CNS metastasis, and intended KRAS G12C inhibitor in the control arm will be used as stratification factors.

KEAP1 mutations are suggested to have a potential prognostic impact on clinical outcomes in patients with NSCLC (Papillon-Cavanagh et al. 2020; Hellyer et al. 2021), and they frequently co-occur with *KRAS G12C* mutations in NSCLC (Arbour et al. 2018). In retrospective analyses, co-mutations in *KRAS G12C* and *KEAP1* have been correlated with reduced overall response rates, PFS, and OS compared to *KRAS G12C, KEAP1* wildtype tumors in patients with NSCLC treated with KRAS G12C inhibitors (Skoulidis et al. 2021; Jänne et al. 2022; Sacher et al. 2023; Negrao et al. 2023a). Prospectively stratifying by *KEAP1* mutation status will minimize the risk of imbalance of this poor prognostic biomarker and prevent *KEAP1*-related confounding effects on the comparison of divarasib's clinical activity to sotorasib's or adagrasib's.

Randomization will also be stratified by history of CNS metastasis. CNS involvement is common in KRAS G12C + advanced NSCLC, occurring in 27–42% of patients (Cui et al. 2020; Sebastian et al. 2021; Wu et al. 2021; Spira et al. 2021), and is associated with a poor prognosis (Parikh et al. 2015; Tomasini et al. 2016; Lauko et al. 2021). Sotorasib and adagrasib have been evaluated in a limited number of patients with untreated or treated brain metastases, and these analyses indicate some evidence of intracranial activity (Ramalingam et al. 2021, Negrao et al. 2023b). However, the intracranial activity

of KRAS G12C inhibitors has not been completely characterized. Therefore, stratifying based on history of CNS metastasis will mitigate the potential for imbalance among participants receiving divarasib and participants receiving the control drugs.

In addition to the stratification factors of *KEAP1* mutation status and history of CNS metastasis, randomization will be stratified by the intended KRAS G12C inhibitor that the participant will receive if randomized to the control arm. Although the mixed control arm includes two drugs with the same mechanism of action (KRAS G12C inhibition) and similar efficacy (Skoulidis et al. 2021; Jänne et al. 2022), there are key differences in the adverse event profile and drug interaction profile that may influence an investigator's choice when selecting between the two (Corral de la Fuente et al. 2022; Lumakras® [sotorasib] Summary of Product Characteristics [SmPC]; Krazati® [adagrasib] SmPC). Furthermore, certain clinical characteristics such as a history of brain metastases, may also have an impact on selection of the control drug (Reck et al. 2021; Riely et al. 2021). Stratifying by intended KRAS G12C inhibitor will allow for balanced subgroups between the participants receiving the individual control drugs and the participants receiving divarasib.

4.2.6 Rationale for Collection of Information on Race and Ethnicity

Data pertaining to participant race and ethnicity represents a component of the broad demographic profile of the study population. Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial, including identification of potential differences in efficacy, safety, and pharmacokinetics among participants. Collection of race and ethnicity data may enable investigation of potential relationships between biomarkers and race or ethnicity, including determination of whether race or ethnicity could be a prognostic factor. Collection of these data may also contribute to a better understanding of the distribution of NSCLC according to race or ethnicity.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

Based on the totality of nonclinical data, clinical safety and activity data, and analyses of clinical exposure–response relationships, including exposure–efficacy and exposure–safety, 400 mg QD of divarasib has been selected for further evaluation in this study. Nonclinical studies with divarasib demonstrate that anti-tumor activity is dependent on the extent of divarasib covalent target engagement, inhibition of the KRAS pathway, and the intrinsic dependence on KRAS G12C in a given tumor context. Less sensitive nonclinical models demonstrate that higher doses of divarasib are required to achieve maximal covalent target engagement and sustained inhibition of cell proliferation, both of which are necessary to achieve anti-tumor activity. Together, these nonclinical data suggest that higher clinical exposures of divarasib capable of maximizing covalent target engagement and inhibition of cellular proliferation may benefit a higher proportion of patients.

From Study GO42144, the observed mean minimum concentration under steady-state conditions ($C_{min,ss}$) in participants treated with 400 mg QD of divarasib was greater than the exposure required to achieve maximal covalent target engagement based on nonclinical models. Based on the $C_{min,ss}$ derived from the preliminary population pharmacokinetic (PK) model, a larger proportion of patients treated with 400 mg QD of divarasib, compared with 200 mg QD, 100 mg QD or 50 mg QD, is predicted to achieve exposures corresponding to maximal covalent target engagement from nonclinical studies. Consistent with the nonclinical data, an analysis of exposure-response showed that a higher $C_{min,ss}$ was correlated with a higher probability of achieving disease control (defined as stable disease or better) and appeared to be associated with a higher probability of partial response (PR) in participants with NSCLC. Common adverse events reported with divarasib, including nausea, vomiting, and diarrhea of any grade, and Grade 3 events did not appear to have a relationship with divarasib dose or exposure. Based on analysis of exposure-adverse event relationships, there was no significant correlation between steady state exposure for maximum concentration observed (C_{max}), area under the concentration–-time curve (AUC), or minimum concentration observed (C_{min}) and the probability of adverse events, including Grade ≥ 2 nausea, vomiting, diarrhea, and ALT and/or AST increased. Furthermore, anti-tumor activity with divarasib as a single agent has been observed at all dose levels evaluated across tumor types, including in NSCLC. In conclusion, the exposure-safety and exposure-efficacy analyses suggest that the 400 mg QD divarasib dose provides better activity without compromising safety compared to lower doses.

In the KRAS G12C + cohort of Study BO29554 (Blood First Assay Screening Trial), participants were randomized to 200 and 400 mg QD divarasib cohorts to evaluate the pharmacokinetics, safety, tolerability, and anti-tumor activity of divarasib. Preliminary data from a pre-specified interim analysis continued to support 400mg QD divarasib as the selected dose for evaluation in this study.

Overall, the available nonclinical and clinical data for divarasib support the further evaluation of 400 mg QD of divarasib in this study.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last scheduled procedure shown in the schedule of activities (see Section 1.3, Table 1).

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last data point required for statistical analysis (i.e., PFS and OS) or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur more than 4 years after the last participant is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

Treatment will continue until disease progression per RECIST v1.1 or, in the case of participants continuing study treatment beyond progression, until loss of clinical benefit. The total duration of study participation for each individual is expected to range from 1 day to more than 4 years.

5. STUDY POPULATION

Approximately 320 participants with previously treated KRAS G12C + NSCLC will be enrolled in this study.

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

5.1 INCLUSION CRITERIA

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

- Signed Informed Consent Form
- Age $\geq$ 18 years at the time of signing Informed Consent Form
- Unequivocal histologically or cytologically confirmed diagnosis of metastatic or locally advanced NSCLC not amenable to treatment with surgical resection or combined chemoradiation
- Disease progression during or after treatment with at least one prior systemic therapy but no more than three lines of prior systemic therapy in the advanced or metastatic setting (with the exceptions for adjuvant/neoadjuvant therapies as outlined below):
  - Prior systemic treatment must include a platinum-based doublet chemotherapy regimen and a PD-L1/PD-1 inhibitor, either given in combination as one line of therapy (i.e., PD-L1/PD-1 inhibitor plus platinum-based doublet chemotherapy) or as individual lines of therapy (i.e., PD-L1/PD-1 inhibitor preceded or followed by platinum-based doublet chemotherapy) unless the individual has a medical contraindication to one of the required therapies. Approved PD-L1/PD-1 inhibitors must have been administered according to local drug prescribing information.
  - Adjuvant/neoadjuvant platinum-based chemotherapy, adjuvant platinum-based chemotherapy followed by immunotherapy, chemoradiation, or chemoradiation followed by immunotherapy qualifies as a prior systemic therapy if $<$ 6 months have elapsed between the last dose and the date of recurrence.
    - If a participant has additional approved standard treatment options available, the study doctor must offer these additional approved treatment options and discuss the risks and benefits of those treatments with the participant before informed consent to participate in this study is obtained. This discussion must be documented in patient records.

- Measurable disease according to RECIST v1.1
- Documentation of the presence of a KRAS G12C mutation through central laboratory testing of a tumor tissue sample or preexisting test results of a blood or tumor tissue sample
  - Preexisting test results in blood or tumor tissue for *KRAS G12C* must be performed using a validated PCR or next-generation sequencing (NGS) assay from an appropriately accredited/certified laboratory (e.g., Clinical Laboratory Improvement Amendments-certified or equivalent). The full legible and de-identified laboratory report of the *KRAS G12C* mutation result must be available and submitted to the Sponsor's designated central laboratory within 30 days of randomization.
  - Participants without preexisting test results for *KRAS G12C* mutation status must submit a representative tumor tissue sample at the time of screening or optional prescreening for central assessment of biomarker eligibility. Central *KRAS G12C* assessment will be done in accordance with local regulations.
- Determination of *KEAP1* mutation status using the Sponsor's designated NGS diagnostic laboratory and test (F1LCDx) or from preexisting results from Sponsor approved NGS tests
  - Blood samples will be collected from all prospective participants with KRAS G12C + tumors for central assessment of *KEAP1* mutation status, even if a prospective participant has a preexisting *KEAP1* result. While central assessment of *KEAP1* mutation status is preferred for stratification, participants may use preexisting test results from Sponsor-approved NGS tests that are performed at an appropriate accredited/certified laboratory. The full, legible, and de-identified NGS report (all pages and attachments) must be submitted to the Sponsor's designated central laboratory within 30 days of randomization. Unknown *KEAP1* results from preexisting NGS tests are not allowed.
  - If central results are available at the time of randomization, participants will be considered to have a *KEAP1* mutation detected if either the central or local preexisting result has a *KEAP1* mutation (detecting a mutation on both tests is not required).
  - Sponsor-approved NGS test for *KEAP1* status must have complete exonic coverage of *KEAP1* and report all variants.
- Availability of a representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or 10–15 (15 preferred) unstained, freshly cut, serial slides with an associated pathology report
  - If < 10 slides are available, the participant may be eligible for the study following consultation with the Sponsor (see Section 8.7 for tumor tissue requirements).
  - The mandatory tumor tissue sample must be confirmed as available during screening and shipped to the central laboratory within 30 days of randomization (if not already sent during screening or optional prescreening for central assessment of biomarker eligibility).

- If archival tumor tissue is unavailable or determined to be unsuitable for required testing, participants may undergo a biopsy at prescreening or screening if the investigator deems it safe and clinically feasible. A biopsy may also be performed at screening for central assessment of biomarker eligibility if a participant's archival tumor tissue test results do not meet eligibility criteria. Refer to Section 8.7 for additional information on collection and analysis of screening samples.

- ECOG Performance Status of 0 or 1
- Life expectancy of $\geq$ 12 weeks
- Adequate hematologic and organ function within 14 days prior to initiation of study treatment, defined by the following:
  - ANC $\geq$ 1500/μL with one exception:

    Participants with benign ethnic neutropenia (BEN) may be eligible: ANC $\geq 1.3 \times 10^9$/L (1300/μL) BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestations (Atallah-Yunes et al. 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.
  - Hemoglobin $\geq$ 9 g/dL without transfusion
  - Platelet count $\geq$ 100,000/μL without transfusion
  - Total bilirubin $\leq 1 \times$ upper limit of normal (ULN)
  - Serum albumin $\geq$ 2.5 g/dL
  - Liver function tests meeting one of the following criteria:
    - AST and ALT $\leq 2.5 \times$ ULN, with ALP $\leq 2.5 \times$ ULN

      or
    - AST and ALT $\leq 1.5 \times$ ULN, with ALP $> 2.5 \times$ ULN

      Patients with documented liver metastases may have AST and/or ALT $\leq 5.0 \times$ ULN.
  - Creatinine clearance $\geq$ 45 mL/min on the basis of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

    An online calculator for the creatinine clearance using the CKD-EPI equation can be found at the following website: https://www.mdcalc.com/calc/3939/ckd-epi-equations-glomerular-filtration-rate-gfr
  - INR $< 1.5 \times$ ULN and aPTT $< 1.5 \times$ ULN

    This applies only to individuals who are not receiving therapeutic anticoagulation. Individuals receiving therapeutic anticoagulation should be on a stable dose for at least 1 week prior to Day 1 of Cycle 1.

- Negative HIV test at screening with the following exception: individuals with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count $\geq 200/\mu L$, and have an undetectable viral load
- Negative hepatitis B surface antigen (HbsAg) test at screening
- Positive hepatitis B surface antibody (HbsAb) test at screening, or a negative HbsAb at screening accompanied by either of the following:
  - Negative hepatitis B core antibody (HbcAb)
  - Positive HbcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) DNA test

  The HBV DNA test must be performed for individuals who have a negative HbsAg test, a negative HbsAb test, and a positive HbcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or a positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test must be performed for individuals who have a positive HCV antibody test.
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception and agree to refrain from donating eggs as defined below:

  Female participants must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 days after the final dose of adagrasib or divarasib, and 7 days after the final dose of sotorasib.

  Participants must refrain from donating eggs during this same period.

  A female participant is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Please see Section 6.8.2.2 and the local prescribing label for sotorasib for information regarding potential drug–drug interactions (DDI) between this drug and hormonal contraceptives.

  For participants receiving sotorasib, hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, male participants must remain abstinent or use a condom during the treatment period and for 5 days after the final dose of adagrasib or divarasib, and 7 days after the final dose of sotorasib to avoid exposing the embryo. Male participants must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

5.2 EXCLUSION CRITERIA

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

- Pregnancy or breastfeeding, or intention of becoming pregnant during the study or within 7 days of the final dose of sotorasib or 5 days of the final dose of adagrasib or divarasib.

  Female participants of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

- Known hypersensitivity to any of the components of divarasib, or sotorasib or adagrasib
- Inability to comply with study and follow-up procedures
- Inability or unwillingness to swallow pills
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Known concomitant second oncogenic driver (including, but not limited to sensitizing *EGFR* mutations, *ALK* rearrangement, *ROS1* rearrangement, *BRAF V600E* mutation, *HER2* mutations, *NTRK* fusions, *RET* fusions, *MET Exon 14* skipping mutations)

  Testing for listed mutations is not required to determine eligibility*, unless explicitly required by local authorities.*

- Mixed small-cell lung cancer or large cell neuroendocrine histology
- Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control)

  Participants with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:

  – Measurable disease outside the CNS
  – No history of intracranial hemorrhage or spinal cord hemorrhage
  – No ongoing requirement for corticosteroids as therapy for CNS metastases, with corticosteroids discontinued for ≥ 2 weeks prior to enrollment and no ongoing symptoms attributed to CNS metastases
  – No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to Day 1 of Cycle 1
  – No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Note: Participants with new asymptomatic CNS metastases detected at screening are eligible for the study after receiving radiotherapy and/or surgery. Following treatment, these participants may be eligible without the need to repeat the additional brain scan, if all other criteria are met.
- Leptomeningeal disease or carcinomatous meningitis
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures biweekly or more frequently

  Indwelling pleural or abdominal catheters are allowed regardless of drainage frequency, provided the participant has adequately recovered from the procedure, is hemodynamically stable, and symptomatically improved
- Any infection that, in the opinion of the investigator, could impact patient safety, or treatment with therapeutic oral or IV antibiotics within 14 days prior to Day 1 of Cycle 1

  In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or those of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).
- Clinically significant history of liver disease, including viral or other hepatitis, or cirrhosis
- Hypercalcemia (ionized calcium >1.5 mmol/L or calcium >12 mg/dL) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab
- Any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination findings, or clinical laboratory findings that give reasonable suspicion of a disease or condition that contraindicates the use of an

investigational drug, that may affect the interpretation of the results, or renders the participant at high risk from treatment complications

- Significant traumatic injury or major surgical procedure within 4 weeks prior to Day 1 of Cycle 1
- Chronic diarrhea, short bowel syndrome, or significant upper gastrointestinal surgery including gastric resection, a history of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) or any active bowel inflammation (including diverticulitis)
- Prior treatment with any KRAS G12C inhibitor or pan-KRAS/RAS inhibitor
- Treatment with anticancer therapy (e.g., chemotherapy, immunotherapy, biologic therapy, or an investigational anticancer agent) within 3 weeks prior to initiation of study treatment.
- More than 30 Gy of radiotherapy to the lung within 6 months of randomization
- Uncontrolled tumor-related pain
  - Participants requiring pain medication must have adequate pain control.
  - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to randomization. Participants should be recovered from the effects of radiation. There is no required minimum recovery period.
  - Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for locoregional therapy, if appropriate, prior to randomization.
- Unresolved toxicities from prior anticancer therapy, defined as not having resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Grade 1 or better, or to levels dictated in the eligibility criteria or toxicities from prior anticancer therapy or palliative radiation therapy that are considered irreversible (defined as having been present and stable for $>$6 months)

  Exceptions of unresolved toxicities include alopecia, vitiligo, or endocrinopathy managed with replacement therapy
- Treatment with strong CYP3A4 inhibitors or inducers (see Section 6.8.2.1) within 14 days or 5 half-lives of the drug or its major active metabolite, whichever is longer, prior to initiation of study treatment
- Any serious medical condition or abnormality in clinical laboratory tests that precludes an individual's safe participation in and completion of the study
- Blood or platelet transfusion within 14 days prior to screening
- History or presence of an abnormal ECG that is deemed clinically significant, (e.g., complete left bundle branch block, second- or third-degree atrioventricular heart block) or evidence of prior myocardial infarction

- History of malignancy within 5 years prior to screening, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, nonmelanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Significant cardiovascular disease, as evidenced by any of the following conditions within 6 months of randomization:
  - QT interval corrected through the use of Fridericia's formula (QTcF) >480 ms demonstrated by at least two ECGs >30 minutes apart.
  - Has clinically significant, uncontrolled, cardiovascular disease, including Grade III or IV congestive heart failure according to the New York Heart Association classification; myocardial infarction or unstable angina within the previous 6 months, uncontrolled hypertension, or clinically significant, uncontrolled arrhythmias, including bradyarrhythmias that may cause QT prolongation (e.g., Type II second-degree or third-degree heart block)
- History of prolonged QT syndrome or torsades de pointes
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Current treatment with medications that are well known to prolong the QT interval (Appendix 9)

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has the following meal and dietary restrictions:

- Refrain from consumption of grapefruit, grapefruit juice, pomelo, or Seville oranges from 7 days before the start of study treatment until after the final dose

5.3.2 Caffeine, Alcohol, and Tobacco

The study has the following alcohol restrictions:

- From screening until completion of the study, participants will drink no more than two servings of alcohol per day (one serving is 12 ounces of beer, 5 ounces of wine, 1.5 ounces of spirits, or equivalent). Participants must agree to abstain from alcohol consumption 12 hours prior to Day 1 of Cycle 1.

This study has no caffeine or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion. Individuals are not required to re-sign the consent form if they are re-screened within 14 days after previously signing the consent form. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

The investigational medicinal products (IMP) for this study are divarasib, sotorasib, and adagrasib. Appendix 10 identifies all investigational medicinal products for this study.

6.1 STUDY TREATMENT ADMINISTERED

Table 3 provides a description of assigned study treatments for this study.

Table 3 Study Treatment Description

<table>
<tr><td></td><td>Divarasib</td><td>Sotorasib</td><td>Adagrasib</td></tr>
<tr><td>Use</td><td>Experimental</td><td>Active comparator</td><td>Active comparator</td></tr>
<tr><td>Drug form</td><td>Tablet</td><td>Tablet</td><td>Tablet</td></tr>
<tr><td>Unit dose strength(s)</td><td>25 mg, 50 mg, 100 mg, 200 mg, 400 mg</td><td>120 mg, 240 mg [a], 320 mg [a]</td><td>200 mg</td></tr>
<tr><td>Dosage level</td><td>400 mg QD</td><td>960 mg QD</td><td>600 mg BID</td></tr>
<tr><td>Formulation</td><td>Refer to pharmacy manual and Divarasib Investigator's Brochure</td><td rowspan="2">Refer to local prescribing information</td><td rowspan="2">Refer to local prescribing information</td></tr>
<tr><td>Packaging</td><td>25 tablets per bottle</td></tr>
<tr><td>Labeling</td><td colspan="3">Per local requirements</td></tr>
<tr><td>Route of administration</td><td>Oral</td><td>Oral</td><td>Oral</td></tr>
<tr><td>Source</td><td>Sponsor</td><td colspan="2">Sponsor or site [b]</td></tr>
</table>

BID = twice daily; QD = daily.

[a] The 240-mg and 320-mg dosage forms can be used in countries/regions if approved by the local Health Authority.

[b] In the US, sotorasib and adagrasib may be provided by the Sponsor centrally or via patient pharmacy cards, or locally by the site.

The treatment regimens are summarized in Section 4.1.

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 4.

6.1.1 Divarasib

Participants will self-administer divarasib at a dose of 400 mg PO QD during each 21-day- cycle (see Section 4.1). For divarasib doses to be administered at home, a sufficient number of tablets should be dispensed to the participant to last until the next visit, or at the investigator's discretion, through one 21-day cycle. Participants will self-administer divarasib at home or in the clinic on specific clinic visit days as detailed below.

Participants should take divarasib at approximately the same time each day unless otherwise instructed. Participants should be instructed on proper pill swallowing without chewing or crushing the tablet*, e.g., it is recommended to take the pill with enough water to aid swallowing.* Divarasib tablets can be taken with or without food. Participants will be instructed as to the number and strength of tablets to take. Participants will be asked to record the time and date that they take each dose in a medication diary.

During clinic visits when PK sampling is scheduled, participants will be instructed to hold the dose of divarasib if the time that the participant would take divarasib is prior to or during the clinic visit, until after blood samples have been obtained for PK and laboratory assessments. After the sample collection, the participants can take divarasib either at the clinic or outside of the clinic to ensure divarasib is taken at approximately the same time each day.

If a participant misses any dose of divarasib (not taken within 6 hours after scheduled dosing time) or vomits up a tablet, he or she should be instructed to skip that dose, document it in the participant's medication diary, and resume dosing with the next scheduled dose. Missed doses will not be made up.

Participants will be instructed to bring their medication diary to each study visit for assessment of compliance. Participants will also be instructed to bring all unused tablets to each study visit or, at the investigator's discretion, at the end of each cycle, for drug accountability.

6.1.2 Sotorasib

Participants will receive sotorasib 960 mg PO QD during each 21-day cycle. Participants will self-administer sotorasib at home or in the clinic on specific clinic visit days as detailed below.

Participants should take the sotorasib dose whole (all tablets at the same time) with or without food at approximately the same time every day.

During clinic visits when PK sampling is scheduled, participants will be instructed to hold the dose of sotorasib if the time that the participant would take sotorasib is prior to or during the clinic visit, until after blood samples have been obtained for PK and laboratory assessments. After the sample collection, the participants can take sotorasib either at the clinic or outside of the clinic to ensure sotorasib is taken at approximately the same time each day.

A medication diary will be provided for participants to record their adherence to the oral medication.

The sotorasib dose should not be taken more than 6 hours later than the scheduled time (based on the previous day's dose). If a participant misses a dose of sotorasib and if less than 6 hours have passed since the scheduled timing of the dosing, the participant should take the dose as normal. If more than 6 hours have passed since the scheduled time of dosing, the participant must not take the dose. Treatment should be continued as prescribed the next day. Missed doses will not be made up.

If vomiting occurs after taking sotorasib, the participant must not take an additional dose on the same day, and should document it in the medication diary and continue treatment as prescribed the next day.

For more details regarding sotorasib administration, refer to the local prescribing information for sotorasib.

6.1.3 Adagrasib

Participants will receive adagrasib 600 mg PO BID during each 21-day cycle. Participants will self-administer adagrasib at home as detailed below, except on specific clinic visit days where participants will be instructed to take their morning dose of adagrasib in the clinic after all predose assessments have been performed.

A medication diary will be provided for participants to record their adherence to the oral medication.

Adagrasib should be taken at the same time every day with or without food. The tablet should be swallowed whole without chewing, crushing, or splitting the tablet.

If vomiting occurs after taking adagrasib, the participant must not take an additional dose and should document it in the medication diary and resume dosing at the next scheduled time. If a dose is inadvertently missed and more than 4 hours have elapsed from the scheduled dosing time, it should be skipped. The participant should resume dosing at the next scheduled time. Missed doses will not be made up.

For more details regarding adagrasib administration, refer to the local prescribing information for adagrasib.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor where required by local regulations. The study site (i.e., investigator or other authorized personnel e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using an interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. Temperature conditions for all IMPs will be monitored during transit, and any discrepancies will be reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor if supplied by the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Divarasib Investigator's Brochure or local sotorasib or adagrasib prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS.

Participants will be randomly assigned to one of two treatment arms: divarasib or locally approved KRAS G12C inhibitor (sotorasib or adagrasib). Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced

assignment to each treatment arm. Randomization will be stratified by *KEAP1* mutation status, history of CNS metastasis, and intended KRAS G12C inhibitor in the control arm (see Section 4.1 for details).

6.4 STUDY TREATMENT COMPLIANCE

When participants self-administer study treatment, compliance will be assessed.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

The dose of divarasib can be reduced up to two times for management of drug-related toxicities, as described in Appendix 4.

Please refer to respective local prescribing information for dose modification guidelines of sotorasib and adagrasib.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to Roche IMP (divarasib) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMP (divarasib) after completing the study if all of the following conditions are met:

- The participant received Roche IMP during study conduct.
- The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

Eligible participants will be provided access to Roche IMP for up to 3 years after completing the study, unless mandated otherwise by local regulations.

A participant will not be eligible to receive Roche IMP (divarasib) after completing the study if any of the following conditions are met:

- The participant was assigned to a treatment arm that did not include a Roche IMP during study conduct.

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for NSCLC.
- The Sponsor has reasonable safety concerns regarding the IMP as a treatment for NSCLC.
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

https://assets.roche.com/f/176343/x/1b18e080e0/2025-revision-roche_global_policy_on_continued_access_to_investigational_interventions.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until the study treatment can no longer be detected systemically (at least 5 days for divarasib; in accordance with institutional guidelines for sotorasib and adagrasib).
3. If requested by the Medical Monitor (determined on a case-by-case basis), obtain a sample for PK analysis within 5 days from the date of the last dose of study treatment for divarasib and in accordance with institutional guidelines for sotorasib and adagrasib.

6.8 CONCOMITANT THERAPY

Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit must be recorded on the Concomitant Medications eCRF(s) along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2.

Use of the following concomitant therapies is permitted as described below:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 6.8.2.2 for additional information regarding potential DDI between hormonal contraceptives and sotorasib).
- Hormone-replacement therapy
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) or surgery as outlined below:
  - In participants without documentation of radiographic disease progression, it is strongly encouraged to maximize supportive care for symptomatic management and to avoid radiotherapy that will interfere with the assessment of tumor target lesions. The need for radiotherapy is generally considered indicative of progressive disease, and the Medical Monitor should be notified if palliative radiotherapy is planned or started.
  - For participants receiving divarasib, interrupt dosing with divarasib 2 days in advance of radiation therapy or surgery and resume dosing 2 days after completion of radiation therapy or recovery from surgery.
  - For participants receiving sotorasib, if he or she requires palliative radiotherapy or surgery during the study, the Sponsor must be informed before therapy initiation at the earliest opportunity. Sotorasib should be paused until after completion of the treatment and for 7 days post-completion of radiation. Resuming the study drug is contingent upon a discussion between the Medical Monitor and the investigator to ascertain the suitability of treatment continuation.
  - For participants receiving adagrasib, in the event that major surgery is needed during study treatment, the participant should, if possible, interrupt dosing with adagrasib 2 weeks in advance of the surgery and resume dosing 2 weeks after completion of the surgery.
- Pain medications administered per standard clinical practice
- Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed when used to prevent skeletal events. Participants on oral bisphosphonate therapy should be without signs of esophagitis.
- Anti-emetic medications may be administered prophylactically before initial treatment with study drugs.

  - For participants receiving divarasib, dexamethasone, ondansetron and similar agents in this class are effective anti-emetic medications based on early clinical experience; prochlorperazine and/or metoclopramide may be effective anti-emetic medications in some participants.
  - For participants receiving sotorasib or adagrasib, refer to the local prescribing information for concomitant administration with anti-emetic medications.
- Anti-diarrheal medications as outlined below:

  Anti-diarrheal medications should not be prophylactically administered prior to initial treatment but may be administered as needed after study treatment initiation. Anticipatory anti-diarrheal medication, such as loperamide, should be provided to study participants (i.e., ensuring participants have access to anti-diarrheal medications if they develop symptoms of diarrhea at home).
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular weight heparin)
  - For participants receiving adagrasib, refer to Section 6.8.2.3 and the local prescribing information for concomitant administration with anticoagulation therapy.
- Vaccinations (such as influenza, COVID-19)

6.8.2 Cautionary Therapy

6.8.2.1 Medications Given with Precaution due to Effects Related to Divarasib

In vitro data suggest that CYP3A4/5 and non-CYP-mediated metabolism may play a significant role in divarasib clearance. Thus, any medication that strongly inhibits or induces this enzyme should be used with caution, including the medications listed below. Divarasib has been shown to induce CYP3A4 mRNA but not protein in vitro. Additionally, in vitro studies using human hepatocytes revealed that M21 (a major circulating metabolite of divarasib; see Divarasib Investigator's Brochure for more details) has the potential to induce CYP3A4 mRNA expression and enzymatic activity. Since a potential DDI due to CYP3A4 induction cannot be ruled out, any medication that is primarily metabolized by this enzyme (i.e., a sensitive CYP3A4 substrate) and for which small changes in exposure may lead to therapeutic failure should be used with caution, including the medications listed below. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with divarasib.

- Strong/moderate CYP3A4 inhibitors, including, but not limited to, the following: atazanavir, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, telithromycin, erythromycin, troleandomycin, fluconazole, itraconazole, ketoconazole, voriconazole, posaconazole, aprepitant, conivaptan, fluvoxamine, diltiazem, nefazodone, mibefradil, verapamil

- Strong/moderate CYP3A4 inducers, including, but not limited to, the following: rifampin, carbamazepine, phenytoin, oxcarbazepine, phenobarbital, efavirenz, nevirapine, etravirine, modafinil, hyperforin (St. John's Wort), and cyproterone

CYP3A4 substrates sensitive to induction, including, but not limited to, the following: alfentanil, budesonide, buspirone, felodipine, everolimus, hormonal contraceptives, lovastatin, quetiapine, sildenafil, simvastatin, sirolimus, tacrolimus

Based on in vitro assays, divarasib was shown to be a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. The effects of P-gp and BCRP modulators on divarasib pharmacokinetics are not known. Any medication that is an inhibitor or inducer of P-gp or BCRP should be used with caution.

- Inhibitors of P-gp: amiodarone, clarithromycin, cobicistat, cyclosporine, dronedarone, erythromycin, itraconazole, ketoconazole, lapatinib, lopinavir and ritonavir, quinidine, ranolazine, saquinavir and ritonavir, verapamil
- Inducers of P-gp: apalutamide, carbamazepine, fosphenytoin, lorlatinib, phenytoin, rifampin, St. John's wort
- Inhibitors of BCRP: curcumin, cyclosporine A, eltrombopag

Based on in vitro assays, divarasib was shown to inhibit P-gp and BCRP transporters. -DDI potential with co-administered P-gp, and BCRP substrates cannot be excluded. Any medication that is an exclusive substrate of P-gp or BCRP with a narrow therapeutic index should be used with caution. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with divarasib.

The above lists of medications are not necessarily comprehensive, refer to the FDA online resource for additional examples at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise if questions arise regarding medications not listed above.

6.8.2.2 Medications Given with Precaution due to Effects Related to Sotorasib

Avoid co-administration of sotorasib with CYP3A4 substrates with narrow therapeutic indices, including but not limited to alfentanil, cyclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus, tacrolimus*, amlodipine, and manidipine*.

Co-administration of sotorasib with a proton pump inhibitor or an H2 receptor antagonist leads to a decrease in sotorasib concentrations. If co-administration of sotorasib with an acid-reducing agent (proton pump inhibitor, H2 receptor antagonist) is required,

sotorasib should be taken with an acidic beverage (such as cola). Alternatively, sotorasib should be taken 4 hours before or 10 hours after administration of a local antacid.

When sotorasib is co-administered with medicinal products metabolized by CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6, appropriate monitoring is recommended.

When sotorasib is co-administered with a BCRP substrate, including but not limited to rosuvastatin, monitor for adverse reactions of the BCRP substrate and refer to the BCRP substrate's local prescribing information for additional details.

Co-administration of sotorasib with P-gp substrates with narrow therapeutic indices is not recommended.

Co-administration of sotorasib with strong CYP3A4 inducers is not recommended because they may decrease sotorasib exposure.

For additional and more complete details regarding potential drug interactions, please refer to the local prescribing information for sotorasib.

6.8.2.3 Medications Given with Precaution due to Effects Related to Adagrasib

Avoid concomitant use of adagrasib with strong CYP3A4 inducers.

Avoid concomitant use of adagrasib with strong CYP3A4 inhibitors until adagrasib concentrations have reached steady state (after approximately 8 days).

Avoid concomitant use of adagrasib with sensitive CYP3A substrates unless otherwise recommended in the local prescribing information for these substrates.

Avoid concomitant use of adagrasib with sensitive CYP2C9 substrates where minimal concentration changes may lead to serious adverse reactions.

Avoid concomitant use of adagrasib with sensitive CYP2D6 substrates where minimal concentration changes may lead to serious adverse reactions.

Avoid concomitant use of adagrasib with P-gp substrates where minimal concentration changes may lead to serious adverse reactions.

Avoid concomitant use of adagrasib with other products with a known potential to prolong the QT interval (see Appendix 9).

For additional and more complete details regarding potential drug interactions, please refer to the local prescribing information for adagrasib.

6.8.2.4 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential DDIs are generally unknown. For participants newly enrolled in the study, herbal therapy should be discontinued prior to initiation of study treatment. For participants already enrolled into the study and currently receiving herbal therapy at the time of this update, a review of concurrent herbal therapy and risk-benefit assessment should be performed by the investigator prior to continuation of herbal therapy.

6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy within 28 days prior to initiation of study treatment and during study treatment
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority-approved or experimental, for various time periods prior to starting study treatment, depending on the agent (see Section 5.2), and during study treatment, until disease progression is documented and the participant has discontinued study treatment with the exception of palliative radiotherapy, radiotherapy to the brain, and local therapy under certain circumstances (see Section 6.8.1 for details)

For additional information regarding medications that are contraindicated with sotorasib or adagrasib, please refer to the local prescribing information.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. Refer to the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment,
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy

- Use of an anticancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to RECIST v1.1 (unless study treatment is continued beyond radiographic progression)
- For participants treated beyond radiographic disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 4.1 for details)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants will return to the clinic for a treatment discontinuation visit ≤28 days after the final dose of study drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Participants who discontinue study treatment for any reason other than progressive disease per RECIST v1.1 will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see Section 1.3).

After treatment discontinuation, information on survival status and new anticancer therapy will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death (unless the participant withdraws consent or the Sponsor terminates the study).

Refer to the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, a treatment discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to

the schedule of activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

If a participant withdraws from the study, the study staff may use a public information source (e.g., county records), if allowed by local laws, to obtain information about survival status.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (e.g., complete blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including results of any standard of care molecular testing for genes or proteins of interest, prior cancer therapies and procedures), reproductive status, and smoking history will be recorded at screening. Results from any standard of care molecular tests performed may be collected for genes or proteins of interest including, but not limited to: EGFR, BRAF, ALK, ROS1, RET, NTRK, MET exon 14, ERBB2, STK11, KEAP, TTF-1 and PD-L1. Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded. Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity at each scheduled or unscheduled visit; treatment decisions will be made according to the clinical assessment and local laboratory test values.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the participant's home to improve access and convenience for participants participating in the study. The Sponsor will select a health-care company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives

written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Section 1.3) will specify the assessments that may be performed by an MN professional. NOTE: MN is not applicable at sites within the European Economic Area *or any other region or country globally where mobile nursing visits are not permitted.*

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Participants will undergo tumor assessments at screening, every 6 weeks (±7 days) for the first 48 weeks following treatment initiation (Day 1 of Cycle 1), and every 9 weeks (±7 days) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 (see Appendix 8), loss of clinical benefit as determined by the investigator, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Thus, tumor assessments are also to continue according to the Schedule of Activities (Table 1) in participants who discontinue treatment for reasons other than disease progression, even if they start new anticancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Participants who are treated beyond disease progression per investigator-assessed RECIST v1.1 will undergo tumor assessments every 6 weeks (±7 days) after initial documentation of progression, or more frequently if clinically indicated, regardless of time in the study until treatment is discontinued (see Section 4.1 for details).

All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined in Section 8.1.1.1.

The participants in this study will be exposed to a considerable annual effective dose of about 136 mSv based on tumor imaging assessments (CT scan of chest and abdomen; CT or MRI of brain) with a total dose of 17 mSv at each assessment, depending on local practice and scanner equipment. This is potentially approximately 1.5 times the exposure these participants would otherwise be subjected to during standard of care treatment. The additional exposure in this study is due to potentially a shorter tumor assessment interval and for brain imaging that would not be considered standard of care. Patients typically undergo tumor assessments after every 2-3 cycles of treatment to assess response and in this study tumor assessments are performed every 2 cycles. The additional brain imaging in this study is to support a number of clinically relevant CNS endpoints where routine/uniform assessment is necessary for all participants.

As the effects of radiation build up over time, it is important to assess the previous radiation exposure of participants. If the prior exposure exceeds the local recommendations, MRI scans may be recommended. This assessment should be performed prior to the tumor assessment during the screening period to avoid a change of methodology during study conduct.

8.1.1.1 Radiographic Assessments

Screening and subsequent assessments must include computed tomography (CT) scans with contrast (per institutional standard operating procedures) of the chest and abdomen. A CT scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. If a CT scan with contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and magnetic resonance imaging (MRI) scans (with contrast, if feasible) of the abdomen and pelvis should be performed. CT or MRI scans of other disease sites should be performed as clinically indicated.

The use of radiopharmaceutical products (e.g., ^{18}F-FDG, Tc-99m, MIBG) and contrast agents (e.g., gadolinium-based or iodinated contrast media) in study imaging assessments will be consistent with standard/local practice and will not involve a route of administration, dose, patient population, or any other factor that significantly increases the risk (or decreases the acceptability of the risk) to participants. The products employed in these procedures will be at the discretion of participating investigators and shall be locally authorized or otherwise used in compliance with local regulations. The results of this study will not be used to support any new indication or change in labeling for these products.

All participants must undergo an MRI or CT scan (with contrast) of the brain at screening and as part of each subsequent tumor assessment. In the event of an equivocal CT scan, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases. Participants with active or untreated CNS metastases are not eligible for the study (see Section 5.2). If previously irradiated brain lesions are categorized as non-target lesions, the lesions should be followed at all subsequent tumor assessments.

At the investigator's discretion, other methods of assessment of disease as per RECIST v1.1 may be used. If a CT scan for tumor assessment is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. Further investigations, such as bone scans and CT scans of the neck, should also be performed if clinically indicated.

All measurable and/or evaluable lesions identified at screening should be re-assessed at subsequent tumor evaluations according to the schedule described above. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Tumor assessments must be continued after disease progression per RECIST v1.1 for participants who receive treatment beyond progression at the frequency described above. The investigator's assessment of overall tumor response at all timepoints should be based on RECIST v1.1 only. Results must be reviewed by the investigator before dosing at the next cycle.

Details regarding imaging procedures will be provided in an imaging manual.

Radiographic images will be collected and sent to an IRF for a quality and completeness check, for BICR, and for temporary storage prior to transferring images to the Sponsor for the long-term retention and eventual secondary/exploratory use.

Radiographic images, whether reviewed locally or centrally, must be evaluated by a qualified, certified expert.

8.1.1.2 Response Evaluation

PFS will be calculated programmatically by the Sponsor on the basis of BICR assessments of response at specified timepoints according to RECIST v1.1 (see Appendix 8). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

Other endpoints (e.g., duration of response [DOR] and *confirmed* objective response rate [ORR]), will be calculated programmatically by the Sponsor on the basis of BICR assessments of response at each specified timepoint.

8.1.2 Clinical Outcome Assessments

Patient-reported outcome (PRO) instruments will be completed to assess the treatment benefit of divarasib compared with sotorasib and adagrasib. In addition, PRO instruments will enable the capture of each participant's direct experience with divarasib compared with sotorasib, and adagrasib.

PRO data will be collected through use of the following instruments: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-LC13 (Appendix 6).

8.1.2.1 EORTC QLQ-C30

The QLQ-C30 is a validated, reliable self-reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix 6). It consists of 30 questions that assess five aspects of participant functioning (physical, emotional, role, cognitive, and social), three symptom scales (Fatigue, Nausea and Vomiting, and Pain), global health status (GHS) and quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the

GHS and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The QLQ-C30 module takes approximately 10 minutes to complete.

8.1.2.2 EORTC QLQ-LC13

The QLQ-LC13 (see Appendix 6) is a self-reported patient reported outcome (PRO) measure. It is composed of 13 lung cancer specific items and includes 11 disease -specific scales and items (dyspnea, coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts, pain medication; Bergman et al. 1994). The QLQ-LC13 has a recall period of 7 days. All 13 items are scored on a 4-point scale that ranges from "not at all" to "very much." The QLQ-LC13 takes approximately 5 minutes to complete.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head and neck, breast or chest wall and regional lymph nodes, and the cardiovascular, dermatologic, respiratory, gastrointestinal, and neurologic systems.

A limited physical examination will include, at a minimum, symptom-directed physical examination. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from abnormalities identified at screening should be recorded in participant notes. New or worsened clinically significant abnormalities i.e., beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF. Limited physical examinations may be performed by an MN professional.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities, i.e., beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Vital signs will include temperature, respiratory rate, pulse rate, oxygen saturation, and systolic and diastolic blood pressure while the participant is in a seated position.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded

as adverse events on the Adverse Event eCRF. Vital sign measurement may be performed by an MN professional.

8.2.3 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints (see Table 1) and may be obtained at unscheduled timepoints as clinically indicated.

All ECG recordings must be performed on a device that is equipped with reliable, automated algorithms for measuring heart rate and ECG intervals and capable of local printing. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Lead placement should be as consistent as possible. ECG recordings should be performed after the participant has been resting in a supine position for at least 10 minutes, and the participant should remain in a supine position during recording. The same positioning should be maintained for each participant throughout the study. ECG recordings should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be performed within 2.5 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

Paper copies of all ECG tracings must be reviewed, annotated to indicate any clinical findings, signed, and dated by a medically qualified member of the site staff. For each timepoint, heart rate, RR interval, PR interval, QRS interval, uncorrected QT interval, and QTcF based on machine readings of ECG tracings should be recorded on the appropriate eCRF. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

If at a particular postdose timepoint the mean QTcF is $>$500 ms or $>$60 ms longer than the baseline value (i.e., last value prior to initiation of study treatment), another ECG must be recorded, ideally within the next 5 minutes, and ECGs should be repeated at least hourly until two successive ECGs show resolution of the findings. A PK sample should be obtained if not already scheduled for that timepoint. Guidelines for management of increases in QT interval are provided in Appendix 4.

8.2.4 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Sample collection may be performed by an MN professional.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.2.6 Clinical Outcome Assessments

PRO instruments will be completed to more fully characterize the safety profile of divarasib compared with sotorasib and adagrasib. In addition, PRO instruments will enable the capture of each participant's direct experience with divarasib compared with sotorasib and adagrasib.

PRO data will be collected through use of the following instruments: Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) and EORTC Item List 46 (IL46).

8.2.6.1 PRO-CTCAE

The PRO-CTCAE is a validated item library that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of 12 symptoms deemed most applicable to the current study treatments has been selected for this study (see Appendix 6). Symptoms have been selected on the

basis of toxicities associated with the drug class, mechanism of action, or mode of administration and known side effects of divarasib, sotorasib, and adagrasib.

8.2.6.2 EORTC IL46

The IL46 is a single question that assesses bother (burden) of treatment. It is rated on a 1 to 4 scale, ranging from "not at all" to "very much." Similarly worded items have been shown to be a valid and useful summary measure of overall adverse event reporting (Pearman et al. 2018). The single-item IL46 question assesses overall side-effect impact.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study treatment, serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) and serious adverse events considered related to Qiagen therascreen *KRAS* RGQ PCR assay (including any device-related procedures) should be reported immediately (i.e., no more than 24 hours after the investigator becomes aware of the event). In addition, during this period, non-serious adverse events considered related to Qiagen therascreen *KRAS* RGQ PCR assay (including any device-related procedures) should be reported within 5 days after the investigator becomes aware of the event (see A3–5). All other medical events occurring in participants during this period are considered preexisting medical conditions and should be recorded as described in Section A3–7.8. All adverse events will be recorded from the start of treatment until 28 days after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available. Non-serious adverse events considered related to Qiagen therascreen *KRAS* RGQ PCR assay (including any device-related

procedures) will be reported within 5 days after the investigator becomes aware of the event.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

The investigator will be informed of any device deficiencies detected at the testing site that might have an impact on clinical study participants (e.g., a test result leading to inappropriate participant management decision). This will enable the investigator to assess for and report any adverse events associated with the device deficiency (see Appendix 3).

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the

use of applicable systems, such as EudraVigilance), Institutional Review Boards or Ethics Committees (IRBs/Ecs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Divarasib	Divarasib Investigator's Brochure
Sotorasib	Sotorasib E.U. Summary of Product Characteristics
Adagrasib	Adagrasib E.U. Summary of Product Characteristics

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives *a* safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 5. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.6)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- Grade ≥3 nausea or vomiting, or diarrhea
- Grade ≥3 hepatitis or elevation in ALT or AST

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 4.

8.3.9 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Plasma samples will be used to evaluate the pharmacokinetics of divarasib as specified in the schedule of activities (see Section 1.3). Samples collected for analyses of divarasib concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Plasma samples may be used to evaluate the pharmacokinetics of adagrasib and sotorasib as specified in the schedule of activities (see Section 1.3). Predose concentration data of adagrasib and sotorasib may be analyzed based on the totality of data. Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g.,

to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

Refer to Section 8.7 and Appendix 7 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood samples for determination of KEAP1 mutation status for participant stratification purposes and may include biomarker assay development

  Analysis of KEAP1 mutation status will be performed using the Foundation Medicine F1LCDx assay for stratification purposes in participants whose tumors are found to be KRAS G12C-positive.

- Blood and plasma samples for exploratory biomarker objectives, including translational research and biomarker assay development
- Archival or freshly collected tumor tissue sample obtained at baseline for determination of *KRAS G12C* mutation status for determining biomarker eligibility and exploratory biomarker objectives, including translational research and biomarker assay development

  A representative FFPE tumor specimen in a paraffin block (preferred) or 10–15 slides (15 preferred) containing unstained, freshly cut, serial sections along with an associated pathology report are required for all participants enrolled on study. Although 10 slides are required, if <10 slides are available, the participant may be eligible for the study following consultation with the Sponsor.

  If participants do not have preexisting results for *KRAS G12C* mutational status, the mandatory tumor tissue specimen must be submitted during optional prescreening or screening for central biomarker assessment of eligibility via the Qiagen therascreen *KRAS* RGQ PCR assay. For participants enrolled based on preexisting test results for *KRAS G12C* mutation status, the mandatory tumor tissue sample must be confirmed available during screening and shipped to the central laboratory within 30 days of randomization.

Tumor tissue should be of good quality, as determined on the basis of total and viable tumor content. Samples must contain a minimum of 500 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core -needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Endobronchial ultrasound (EBUS)-transbronchial needle aspiration is acceptable (particularly if a larger needle is used), provided tissue is of good quality as described above (i.e., minimum number of 500 viable tumor cells with preserved cellular context and tissue architecture). For EBUS-needle aspirations, an 18-guage or larger needle is recommended. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone is not acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, the participant may undergo a biopsy during screening or prescreening if the biopsy site is safely accessible and deemed clinically feasible. A pre-treatment tumor biopsy may also be performed if an individual's archival tissue test results do not meet eligibility criteria.

Central analysis of KRAS G12C mutation status will be performed using the Qiagen therascreen *KRAS* RGQ PCR assay, an FDA-approved and CE Marked In Vitro Diagnostic device, which may be considered investigational per local regulations.

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.10.

Biomarker research may include, but will not be limited to, analysis of ctDNA levels, analysis of copy number and mutational analyses of cancer-related genes, gene signatures associated with tumor cancer biology, immunobiology and drug activity (like MAPK pathway suppression), changes in cytokines and analysis of other safety biomarkers, potential predictive biomarkers of response and mechanisms of resistance. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of gene and/or protein expression, analysis of mutations, copy number, single nucleotide polymorphisms, and other genomic variants; and genomic profiling. Blood samples may be processed to obtain PBMCs and their derivatives (e.g., DNA or RNA).

Genomic research with a focus on somatic variants may be conducted by comparing DNA extracted from blood or PBMCs with DNA extracted from tissue to distinguish somatic variants from germline variants. Genomic profiling may include WGS or WES of tissue, plasma, and blood samples, with a focus on somatic variants. WGS or WES of blood samples with a focus on germline variants may also be conducted, but only at participating sites (see Section 8.10.1).

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator may obtain an NGS report through Foundation Medicine's web portal. If permitted by local law, the investigator may share and discuss the results with the participant, unless the participant chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. The report may be included in the participant's medical record. Results will not be available for samples that do not meet criteria for testing.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 1 and Table 2). Sample collection may be performed by an MN professional. Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for any remaining blood, plasma, PBMCs, and tumor tissue samples to be stored for optional exploratory research (see Section 8.10.3), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the following exceptions:

- For enrolled participants, remaining archival tissue blocks will be returned to the site upon request or no later than completion of the final Clinical Study Report, whichever occurs first. For individuals who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants unless required by law with the exception of the report from Foundation Medicine. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

8.9.1 EuroQol EQ-5D-5L

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 6). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale that measures health state. The EQ-5D-5L is designed to capture a participant's current health status. Published weighting systems allow for the

creation of a single composite score of the participant's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.10.1 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing with a Focus on Germline Variants (Participants at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will include exploration of germline variants.

The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 8.10.1) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Appendix 1).

8.10.2 Tumor Biopsies (Participants Providing Separate Consent)

Consenting participants will undergo an optional tumor biopsy at the time of disease progression (if deemed clinically feasible by the investigator). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. If an optional biopsy is performed, the FFPE tumor specimen in a paraffin block (preferred) or 10 slides containing unstained, freshly cut, serial sections along with an associated pathology report should be submitted. If tissue is not limiting, a fresh frozen sample (snap frozen) is also requested. Tumor tissue should be of good quality based on total and viable tumor content. Samples must have greater than 20% tumor content with preserved cellular context and tissue architecture.

The Informed Consent Form will contain a separate section that addresses optional biopsies. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of undergoing optional biopsies. Participants will be told that they are free to choose not to undergo optional biopsies and may withdraw their consent at any time and for any reason. A separate, specific signature will be required to document a participant's agreement to undergo optional biopsies. Participants who choose not to undergo optional biopsies will not provide a separate signature. The investigator should document whether or not the participant has given consent to undergo optional biopsies and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

Samples may be used for exploratory biomarker research as described in Section 8.7. Tumor specimens may be used for centralized retrospective assessment to evaluate correlation between immune cells, genes, proteins, DNA, and RNA relevant to the signaling pathways associated with sensitivity/resistance to the investigational agents.

NGS may be performed by Foundation Medicine on disease progression biopsies. If additional fresh frozen tumor specimens are available, samples may be processed to enable single cell analysis and/or establish patient-derived xenograft (PDX) models. Samples may be processed to enable analysis of tumor intrinsic changes and changes within the tumor microenvironment. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 8.7 for information on duration of sample storage and availability of data from biomarker analyses.

8.10.3 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.10.3.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.3.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10.3) will not be applicable at that site.

8.10.3.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to divarasib, diseases, or drug safety:

- Any remaining blood, plasma, PBMCs, and tumor tissue (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.3.4 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by law, with the

exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.3.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period.
A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.3.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples (i.e., all biological material) will be destroyed. However, if RBR samples have been

tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.3.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The purpose of this study is hypothesis testing, testing superiority of divarasib compared with the locally approved KRAS G12C inhibitors with respect to PFS. The null (H_0) and alternative (H_1) hypotheses regarding PFS in the FAS will be tested at a two-sided significance level of 0.05 and can be phrased in terms of the population hazard ratio (HR) λ between the experimental arm and the control arm:

$$H_0: \lambda = 1 \text{ versus } H_1: \lambda \neq 1$$

Null and alternative hypotheses of a similar form will be tested for the key secondary efficacy analyses for OS and time to confirmed deterioration (TTCD).

For *confirmed* ORR, the following null (H_0) and alternative (H_1) hypotheses will be tested at a significance level of 0.05:

$$H_0: p_{\text{experimental}} = p_{\text{control}} \text{ versus } H_1: p_{\text{experimental}} \neq p_{\text{control}}$$

where $p_{experimental}$ and $p_{control}$ refer to the proportion of participants with *a confirmed* objective response in the experimental and the control arms, respectively.

All hypothesis tests will be two-sided unless stated otherwise.

To control the overall level of significance at a two-sided error rate of 0.05, comparisons with respect to PFS, OS, *confirmed* ORR, and TTCD will be conducted hierarchically as follows:

- The primary endpoint PFS will be tested first at an overall two-sided α level of 0.05. If the two-sided p-value corresponding to the stratified log-rank test is less than 0.05, the null hypothesis will be rejected, and it will be concluded that divarasib prolongs duration of PFS relative to sotorasib and adagrasib.
- If divarasib significantly prolongs PFS, then OS will be tested at an overall two-sided α level of 0.05. One interim OS analysis will be performed at the time of the primary PFS analysis. Stopping boundaries for interim and final OS analyses are provided in Section 9.4.

  If divarasib has no significant effect on PFS, then OS will not be tested.
- If divarasib significantly prolongs OS, then *confirmed* ORR will be tested at an overall two-sided a level of 0.05.

  If divarasib has no significant effect on OS, then *confirmed* ORR will not be tested.
- If divarasib significantly improves *confirmed* ORR, then TTCD will be tested at an overall two-sided α level of 0.05 for selected scales in the following hierarchical order (each scale tested only if preceding scale was tested statistically significant):
  - Cough (EORTC QLQ-LC13)
  - Dyspnea (EORTC QLQ-C30)
  - Physical functioning (QLQ-C30)

  For each scale, if the two-sided p-value corresponding to the stratified log-rank test is less than 0.05, the null hypothesis will be rejected, and it will be concluded that divarasib prolongs duration of TTCD relative to sotorasib and adagrasib for this scale.

  If divarasib has no significant effect on *confirmed* ORR, then TTCD will not be tested.

The formal testing for *confirmed* ORR and TTCD will be performed once statistical significance is reached for OS (at the time of interim or final OS analysis), based on the data from the primary PFS snapshot.

9.1.1 Sample Size Determination

A total of approximately 320 participants will be enrolled in this study and randomized in a 1:1 ratio to either divarasib or locally approved KRAS G12C inhibitor (sotorasib or adagrasib). The sample size is determined by the primary endpoint, PFS, and the key secondary endpoint, OS.

The enrollment is projected to complete approximately 14 months after randomization of the first participant with a peak recruitment rate of 32 participants per month. An annual dropout rate of 10% for both arms is assumed. On that basis, it is projected that the primary PFS analysis will occur approximately 24 months after randomization of the first participant and that the final OS analysis will occur approximately 47 months after randomization of the first participant.

The estimates of the number of events required to demonstrate efficacy with regards to PFS are based on the following assumptions:

- Two-sided significance level of 0.05
- 90% power to detect a hazard ratio of 0.64, corresponding to an improvement in median PFS from 7 months to 10.9 months
- The primary analysis of PFS will be conducted when approximately 216 PFS events are observed.
- Under these assumptions, the minimal detectable difference will be a hazard ratio of 0.766 corresponding to an improvement in median PFS from 7 months to approximately 9.1 months.

The estimates of the number of events required to demonstrate efficacy with regard to OS are based on the following assumptions:

- Two-sided significance level of 0.05
- 80% power to detect a hazard ratio of 0.69, corresponding to an improvement in median OS from 13 months to 18.8 months
- One interim analysis for OS at the time of the primary PFS analysis (when approximately 66% of the total OS events have occurred), with use of the Lan-DeMets approximation to the O'Brien-Fleming boundaries (for details see Section 9.4)
- The final OS analysis will be conducted when approximately 231 OS events are observed.
- Under these assumptions, the minimal detectable difference at the final OS analysis will be a hazard ratio of 0.769 corresponding to an improvement in median OS from 13 months to approximately 16.9 months.

The assumptions for median PFS and median OS in the control arm used for sample size calculation are derived from the Phase II studies CodeBreak 100 (median PFS: 6.8 months, median OS: 12.5 months; Skoulidis et al. 2021) and KRYSTAL-1 (median PFS: 6.5 months, median OS: 12.6 months; Jänne et al. 2022). In a conservative approach, given that CodeBreak 100 and KRYSTAL-1 are single arm Phase II studies, median PFS and median OS for the shared control arm are assumed to be slightly higher than results observed for the individual drugs (sotorasib and adagrasib).

9.2 ANALYSIS SETS

The analysis sets for the purposes of analyses are defined in Table 4.

Table 4 Analysis Sets

Analysis Set	Description
Full analysis set	All randomized participants; participants will be included in the analyses according to the treatment to which they were assigned.
Safety analysis set	All participants exposed to study treatment; participants will be analyzed according to the treatment that they actually received.
Response-evaluable set	All participants in the full analysis set with measurable disease at baseline; participants will be included in the analyses according to the treatment to which they were assigned.
PK-evaluable set	All participants who received at least one dose of study drug and had at least one post-baseline quantifiable PK sample available; participants will be analyzed according to the treatment that they actually received.

PK = pharmacokinetic.

9.3 STATISTICAL ANALYSES

The Statistical Analysis Plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. The analyses specified in the Statistical Analysis Plan supersede those specified here.

9.3.1 General Considerations

The efficacy analyses will be performed in the full analysis set, unless otherwise stated, with participants grouped according to the treatment arm to which they were assigned.

Safety and tolerability analyses will be performed on the safety analysis set, with participants grouped according to the treatment that they actually received.

9.3.2 Estimation Methods for the Primary Estimand

The attributes describing the estimand related to the primary analysis are summarized in Section 3.1. The primary efficacy endpoint is PFS, as determined by BICR.

Data for participants without the occurrence of disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

For both intercurrent events, a treatment policy strategy will be applied, i.e., PFS will be assessed irrespective of whether a participant discontinued early from study drug or started non-protocol anticancer therapy prior to disease progression. Tumor

assessments will be performed as per the schedule of assessments until disease progression or death, irrespective of the occurrence of any of the intercurrent events. The investigators will be instructed accordingly.

The primary comparison of interest is the stratified log-rank test (two-sided at 5% significance level) for PFS. The stratification factors are the randomization factors as recorded in IxRS. Results from an unstratified log-rank test will also be presented. The hazard ratio for PFS will be estimated using a stratified Cox regression model in order to provide an estimate of the treatment effect. A 95% confidence interval for the hazard ratio will be provided.

The Kaplan-Meier method will be used to estimate the median PFS for each arm with 95% confidence limits, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment arms. The Brookmeyer-Crowley method will be used to construct the 95% confidence interval for the median PFS (Brookmeyer and Crowley 1982).

A sensitivity analysis will be performed for PFS as determined by the investigator. Also, the impact of missing scheduled tumor assessments on PFS will be assessed by performing a sensitivity analysis based on the interval censoring analysis methods. Additional sensitivity analyses may be added and more details for sensitivity analyses will be provided in the Statistical Analysis Plan.

9.3.3 Estimation Methods for the Secondary Estimands/Endpoints

9.3.3.1 Analysis of the Key Secondary Endpoints

The attributes describing the estimands related to the key secondary objectives are summarized in Section 3.2. The key secondary efficacy endpoints are OS, *confirmed* ORR, and TTCD.

For the analysis of OS, data for participants who are not reported as having died as of the clinical data cutoff date will be censored at the date when they were last known to be alive (or at the time of randomization plus 1 day if no survival follow-up is available after the baseline visit).

For both intercurrent events, a treatment policy strategy will be applied, i.e., OS will be assessed irrespective of whether a participant discontinued early from study drug or started non-protocol anticancer therapy.

Estimation methods will be performed as described for the primary estimand (see Section 9.3.2). The primary comparison of interest is the stratified log-rank test (two-sided 5% significance level) for OS. Critical values at the interim and the final analyses are provided in Section 9.4.

Confirmed ORR is defined as the proportion of participants with a complete response or partial response *on two occasions* ≥4 weeks apart, as assessed by BICR according to RECIST v1.1. Participants not meeting this criterion (including participants without a post-baseline tumor assessment) will be considered non-responders. *Confirmed* ORR will be analyzed on the response-evaluable set (see Table 4).

For both intercurrent events, a composite variable strategy will be applied. Participants who discontinued early from study drug or started non-protocol anticancer therapy prior to achieving *confirmed* objective response will be considered non-responders.

Estimation methods for *confirmed* ORR will be provided in the Statistical Analysis Plan.

TTCD will be assessed irrespective of whether a participant discontinued early from study drug (i.e., treatment policy strategy), and as if no non-protocol anticancer therapy is started prior to a confirmed clinically meaningful deterioration (i.e., hypothetical strategy). A while-alive strategy will be applied for participants who die before reporting any clinically meaningful deterioration. Consequently, the collection of QoL assessments will be continued until clinically meaningful deterioration, start of non-protocol anticancer therapy or death, whichever is earlier, irrespective of study drug discontinuation. The investigators will be instructed accordingly.

For the analysis of TTCD, participants without confirmed clinically meaningful deterioration as of the clinical data cutoff date (including participants who die without reported clinically meaningful deterioration) will be censored at the time of the last assessment (or at the time of randomization plus 1 day if no assessment was performed after the baseline visit). Participants who start non-protocol specified anticancer therapy will be censored at the time of the last assessment before starting the non-protocol specified anticancer therapy.

Estimation methods will be performed as described for the primary estimand (see Section 9.3.2). The primary comparison of interest for TTCD is the stratified log-rank test (two-sided 5% significance level). TTCD will be analyzed at the time when OS analysis shows statistical significance.

Sensitivity analyses for OS, *confirmed* ORR, and TTCD will be described in the Statistical Analysis Plan.

9.3.3.2 Other Secondary Endpoints

Duration of Response (DOR) is defined as the time from the first occurrence of a documented *confirmed* objective response until the first date that progressive disease or death is documented, whichever occurs first. Disease progression will be determined by BICR according to RECIST v1.1. DOR will be assessed in participants who had *a confirmed* objective response during the study as determined by BICR. Participants who have not progressed and who have not died as of the clinical data cutoff date for

analysis will be censored at the time of the last tumor assessment (or at the date of first *confirmed* objective response plus 1 day if no tumor assessment was performed after the *confirmed* objective response).

The DOR analysis will be performed on the basis of a non-randomized subset of participants (specifically, participants who achieve *a confirmed* objective response); therefore, formal hypothesis testing will not be performed for this endpoint. DOR will be estimated using Kaplan-Meier methodology. Comparisons between treatment arms will be made for descriptive purposes only.

For endpoints collected using EORTC QLQ-C30 and QLQ-LC13 mean scores and changes from baseline will be analyzed descriptively for each timepoint, with baseline defined as the last assessment prior to start of study treatment. TTCD analyses for scales that are not considered key secondary endpoints will be performed as described for TTCD key secondary endpoints in Section 9.3.3.1.

9.3.3.3 Safety and Tolerability Analyses

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, etc.) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, oxygen saturation, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

PRO-CTCAE analyses will be primarily descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities during the study. PRO-CTCAE data will be analyzed at the item level.

PRO-CTCAE data will be summarized over time. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data.

The number and percentage of participants reporting each symptom and the change from baseline by category (frequency of occurrence, severity, and interference) will be summarized at each assessment timepoint by treatment arm. For items that are rated on a 5-point Likert scale, the maximum post-baseline score and change from baseline will be summarized by treatment arm.

Graphical representation of PRO-CTCAE data over time will also be provided.

The analyses of the EORTC IL46 item will be descriptive, with a focus on characterizing the pattern of being troubled by side effects from treatment over the course of the study. The number and percentage of participants reporting each response option ("Not at all" to "Very much") to the item and the change from baseline by response option will be summarized at each assessment timepoint by treatment arm. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data.

9.3.4 Exploratory Analyses

The probability of CNS progression, non-CNS progression, and death will each be estimated using cumulative incidence functions. CNS progression will be defined as progression due to newly developed CNS lesions and/or progression of previously treated CNS lesions. Estimates of the CNS progression rates at 6 and 12 months with 95% confidence intervals determined on the basis of cumulative incidence functions will be presented.

Time to CNS progression as determined by BICR according to RECIST v1.1, is defined as the time from randomization until first radiographic evidence of CNS progression. To account for the competing risks inherent in such an analysis, hazard ratios will be computed on the basis of cause-specific hazard functions.

Intracranial PFS will be estimated using Kaplan-Meier methodology.

Exploratory biomarker analyses will be performed in an effort to understand the association of biomarkers with study drug response, including but not limited to efficacy and/or adverse events, as well as emergence of resistance. Additional pharmacodynamics analyses will be conducted as appropriate. Exploratory biomarker analyses will include assessments of biomarkers in both tumor tissue and blood. Such assessments will include but will not be limited to mutational analysis using NGS and gene expression and may also include other methods that may become available in the future.

Health utility data from the EuroQol EQ-5D-5L will be evaluated in pharmacoeconomic models. Results from health economic data analyses will be reported separately from the Clinical Study Report.

9.3.5 Other Analyses

9.3.5.1 Summaries of Conduct of Study

Enrollment, study drug administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study drug discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.3.5.2 Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, race/ethnicity, baseline disease characteristics, ECOG Performance Status, and number of prior cancer treatments) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.3.5.3 Pharmacokinetic Analyses

Individual plasma concentrations of divarasib will be listed and summarized. Divarasib PK data may be pooled and analyzed using the population PK analysis approach, as appropriate, and reported separately from the study report.

Individual plasma concentrations of sotorasib and adagrasib may be listed and summarized. Additional PK analyses (e.g., ex vivo unbound plasma concentration analysis for divarasib, sotorasib, adagrasib) may be conducted as appropriate.

9.4 INTERIM ANALYSIS

One interim analysis on OS will be performed at the time of the primary PFS analysis. The Lan-DeMets alpha spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994).

The expected number of OS events at the time of the interim analysis is approximately 153 (i.e., 66% information fraction), leading to a stopping boundary in terms of p-value $\leq$ 0.0116 at the interim analysis. Under these assumptions, the critical value for the final OS analysis will be a p-value of 0.0464.

Critical values at the interim and the final analyses will be adjusted according to the actual number of observed OS events per stage to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

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

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice
- Applicable laws and regulations.

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

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

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 250 sites globally will participate to enroll approximately 320 participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An independent Data Monitoring Committee will be employed to monitor and evaluate participant safety throughout the study. An independent review facility will collect, store, and potentially review imaging data.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data and data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

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

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

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

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

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

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

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY *AND PROTECTION OF TRADE SECRETS*

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells) • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine (serum), total protein, albumin (serum), phosphate, calcium, *ALP, ALT, AST,* total and direct bilirubin *(for all participants, both total and direct bilirubin may be performed at each visit; however, only total bilirubin is required if results are within normal range. If total bilirubin is out of range, then direct bilirubin must be performed).* • *Urate or uric acid* • *Lactate dehydrogenase (LDH)* • Lipase • Coagulation: INR and aPTT • HIV serology: HIV-1/2 antibody • HBV serology: HbsAg, HbsAb, and total HbcAb for all individuals; HBV DNA for individuals with negative HbsAg and HbsAb tests and a positive total HbcAb test • HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test • Pregnancy test All female participants of childbearing potential will have a serum pregnancy test performed at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, nitrites, leukocyte esterase, and blood)

HbcAb = hepatitis B core antibody; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus.

Investigators must document their review of each laboratory safety report.

Appendix 3
Safety Parameters: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

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

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3-3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the electronic Case Report Form (eCRF) (Table A3-1).

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event. Serious adverse events (SAEs) should always be reported, even if they are not severe; are CTCAE Grade 1 or 2; and are not possibly related to study drugs.

Table A3-1 Timeline and Mechanism for Collecting and Reporting Adverse Events

Adverse Event (Initial and Follow-Up Information)	Collection Period		Reporting Timeline (Investigator's Awareness to Sponsor)	Collection Mechanism	
	Start	Stop		Primary	Back-Up [a]
AE related to IVD protocol-mandated procedure in a user or other person [b]	First participant screened	End of study	5 days	Medical Device Adverse Event and Device Deficiency Form	NA
SAE related to IVD protocol-mandated procedure in a user or other person [b]	First participant screened	End of study	Immediately (no later than 24 hours)	Medical Device Adverse Event and Device Deficiency Form	NA
AE related to any protocol-mandated IVD procedure in a participant	Signed ICF	Initiation of study treatment	5 days	Screening Adverse Event eCRF	Medical Device Adverse Event and Device Deficiency Form
SAE related to any protocol-mandated procedure (including an IVD procedure) in a participant	Signed ICF	Initiation of study treatment	Immediately (no later than 24 hours)	Screening Adverse Event eCRF	Clinical Trial Adverse Event/ Special Situations Form
AE related to any protocol-mandated IVD procedure in a participant	Initiation of study treatment	*28* days after final dose of study treatment	5 days	Adverse Event eCRF	Medical Device Adverse Event and Device Deficiency Form

Appendix 3: Safety Parameters: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Adverse Event (Initial and Follow-Up Information)	Collection Period		Reporting Timeline (Investigator's Awareness to Sponsor)	Collection Mechanism	
	Start	Stop		Primary	Back-Up [a]
AE regardless of causal relationship in a participant	Initiation of study treatment	*28* days after final dose of study treatment *or until they receive another anti-cancer therapy, whichever occurs first*	NA	Adverse Event eCRF	NA
AESI or SAE regardless of causal relationship in a participant	Initiation of study treatment	*28* days after final dose of study treatment *or until they receive another anti-cancer therapy, whichever occurs first*	Immediately (no later than 24 hours)	Adverse Event eCRF	Clinical Trial Adverse Event/ Special Situations Form

AE = adverse event; AESI = adverse event of special interest; DLAE = dose-limiting adverse event; DLT = dose-limiting toxicity; eCRF = electronic Case Report Form; EDC = electronic data capture; ICF = Informed Consent Form; IVD = in vitro diagnostic; NA = not applicable; SAE = serious adverse event.

[a] Back-up mechanism should only be used if the EDC system is not available. Once the EDC system is available, all information will need to be entered as soon as possible and submitted via the EDC system.

[b] Any person other than the clinical trial participant.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table A3-2 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A3-2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator should report in the eCRF any postmortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately

(i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information

on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS, MEDICAL DEVICE ADVERSE EVENTS, AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) and serious adverse events considered related to the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures) should be reported immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) using the Screening Adverse Event eCRF or using the paper Clinical Trial Adverse Event/Special Situations Form if the EDC is not available.

In addition, during this period, non-serious adverse events considered related to the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies) should be reported within 5 days after the investigator becomes aware of the event using the Screening Adverse Event eCRF or the paper Investigational Medical Device Adverse Event and Device Deficiency Form if the EDC system is not available.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, all adverse events including serious adverse events, adverse events of special interest will be reported until 28 days after the final dose of study treatment or until they receive another anti-cancer therapy, whichever occurs first. Also, after initiation of study treatment, all non-serious medical device adverse events that are considered related will be reported until 28 days after the final dose of study treatment. For serious adverse events and adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF. For non-serious medical device adverse events that are considered related the

Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures and adverse events that may be a consequence of device deficiencies), investigators should record all case details within 5 days on the Adverse Event eCRF. Reports will be submitted via the electronic data capture (EDC) system and will be sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form (all serious adverse events) or Investigational Medical Device Adverse Event and Device Deficiency Form (non-serious investigational medical device related), using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting events that occur more than 28 after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event *collection* period (defined as 28 after the final dose of study treatment), all deaths, regardless of cause, should be *documented as described in* the eCRF *Completion Guidelines*.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment or the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures), the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event /Special Situations Form (study drug related events) or Investigational Medical Device Adverse Event and Device Deficiency Form (medical device related), using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and

concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.2 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.4 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a

descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.5 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.6 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury

(as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.7 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1) that are attributed by the investigator solely to progression of non–small cell lung cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.8 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.9 LACK OF EFFICACY OR WORSENING OF NON–SMALL CELL LUNG CANCER

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of non–small cell lung cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of non–small cell lung cancer"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on Response Evaluation Criteria in Solid Tumors, Version 1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A3–7.10 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition

  - The participant has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.11 PARTICIPANT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from PRO-CTCAE or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile participant reports of treatment-related symptoms (via PRO-CTCAE) with investigator reports of adverse events. Sites are not expected to review the PRO-CTCAE or other PRO data for adverse events.

A3–7.12 SAFETY BIOMARKER DATA

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

A3–8 SPECIAL SITUATIONS (OVERDOSE, MEDICATION ERROR, DRUG ABUSE, AND/OR DRUG MISUSE)

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse} (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

After initiation of study drug, special situations associated with divarasib, sotorasib, and adagrasib and any associated adverse events will be reported until 28 after the final dose of study drug.

Special situations, regardless of whether they result in an adverse event, should be reported on the Special Situations eCRF. If there are any associated adverse events, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated adverse events should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section A3–5.

A3–9 MEDICAL DEVICE ADVERSE EVENTS

This study will comply with International Standard (ISO) 20916 on in vitro diagnostic medical devices—clinical performance studies using specimens from human subjects—good study practice and Regulation (EU) 2017/746 on in vitro diagnostic medical devices requirements for medical device adverse event collection and reporting for events associated with the use of the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures) (see also Sections 8.3.1, 8.3.2, A3–5, and A3–6).

A3–9.1 DEFINITION OF IVD MEDICAL DEVICE ADVERSE EVENT

Any untoward medical occurrence, inappropriate patient management decision, unintended disease or injury, or untoward clinical signs in subjects, users, or other persons, with any connection to study related activities, whether or not related to the IVD medical device under investigation. Adverse events can be caused by, for instance, insufficient or inadequate instructions for use, deployment, installation, operation, or any malfunction of the IVD medical device under investigation. This definition includes the malfunction or deterioration of a device which has not yet caused death or serious injury, but which could lead to death or serious injury. This definition is not intended to be used in determining whether an event is reportable to a regulatory authority. For users or other persons, this definition is restricted to events related (defined as possible, probable, or causal relationship) with the investigational IVD medical device or device-related procedures. False negative or false positive results are not considered

an adverse event unless in an interventional study, inappropriate patient management decisions are made based on those false results.

A3–9.2 DEFINITION OF DEVICE DEFICIENCY

A device deficiency is any inadequacy in the identity, quality, durability, reliability, usability, safety, or performance of an investigational medical device, including malfunction of the device, use error, or inadequate manufacturer-supplied instructions (including labeling) for use, deployment, installation, or operation of the device (see Section 8.3.2).

A3–9.3 ASSESSMENT OF CAUSALITY OF MEDICAL DEVICE ADVERSE EVENTS

The circumstances surrounding the event, an evaluation of any potential alternative causes, and any knowledge about the clinical study participant, user, or other person should be used to determine whether an adverse event is considered to be related to the use of the Qiagen therascreen KRAS RGQ PCR assay (including any device-related procedures). The guidance provided below should be used to assess the causality of these adverse events.

Relationship	Criteria for Classification
Not related	The relationship of the event to the device or device-related procedures can be excluded when • The event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device; the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • The serious adverse event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • The event does not depend on a false result given by the investigational device used for diagnosis, when applicable. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Relationship	Criteria for Classification
Probable	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Causal	The adverse event/serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when • The event is a known side effect of the specimen collection procedures for the investigational IVD; • The event has a temporal relationship with investigational device use/application or procedures; • The serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); • Other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • Harm to the subject is due to error in use; • The event depends on a false result given by the investigational device used for diagnosis, when applicable. In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Note: Events associated with a procedure that would have been performed in a clinical study participant with or without use of the device should be classified as not related.

A3–9.4 REPORTING MEDICAL DEVICE ADVERSE EVENTS

See Section A3–5 for details on reporting medical device adverse events in participants. User injury adverse events must be reported using the paper Investigational Medical Device Adverse Event and Device Deficiency Form.

Appendix 4
Safety Plan: Management of Identified and Potential Risks

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A4–1 RISKS ASSOCIATED WITH DIVARASIB

Divarasib is not approved by health authorities, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with divarasib in completed and ongoing studies. The anticipated important safety risks for divarasib are outlined below. Please refer to the current Divarasib Investigator's Brochure for a complete summary of safety information.

A4–1.1 GASTROINTESTINAL TOXICITIES (DIARRHEA, NAUSEA, VOMITING)

In 4-week toxicology studies in cynomolgus monkeys with divarasib, clinical signs of gastrointestinal intolerance with retching and vomiting were observed. Diarrhea, nausea, and vomiting have been reported in patients treated with divarasib. Please refer to the Divarasib Investigator's Brochure for additional information.

Gastrointestinal (GI) toxicities (e.g., diarrhea, nausea, vomiting) *are very commonly (≥1/10)* reported in association with the KRAS G12C inhibitors, sotorasib (*LumaKRAS® SmPC*) and adagrasib (*Krazati® SmPC).*

The mechanism of action underlying GI toxicities reported with oral KRAS G12C inhibitors remains unknown. Patients should be closely monitored for signs and symptoms related to gastrointestinal effects.

Development of abdominal pain, nausea, vomiting, and clinically significant changes in stool (e.g., diarrhea, bloody stools) may necessitate more frequent monitoring, and study drug may be held if symptoms are prohibitive for normal function. Clinical evaluation for infectious (e.g., *Clostridium difficile*, enteric bacteria, and cytomegalovirus) or inflammatory (e.g., inflammatory colitis) etiologies for diarrhea should be conducted with additional consideration for gastrointestinal consultation as needed. Participants should be made aware of the risk for diarrhea, nausea, and vomiting and should be instructed to inform their treating physician and to initiate anti-emetic or anti-diarrheal medications as soon as possible if they experience these events. Participants should be treated and managed per standard of care and per protocol guidelines (see A4–4.3.1), including early or prophylactic use of anti-emetics, early use of anti-diarrheals, probiotics, and appropriate supportive care including hydration and dietary modification if clinically indicated. Participants should be reassessed within 24 hours of new or worsened symptoms, or initiation or change in supportive care measures, to ensure adequate improvement.

A4–1.2 ELEVATION OF HEPATIC TRANSAMINASES

In cynomolgus monkeys, minimal to mild transaminase elevation has been observed after administration of divarasib *(Study 19-0962).*

Hepatic transaminase elevation is very commonly (≥1/10) reported in association with the KRAS G12C inhibitors *sotorasib (LumaKRAS® SmPC) and adagrasib (Krazati® SmPC).*

Participants will be monitored routinely with chemistry panels that include liver function tests and for signs or symptoms of hepatic pathology (e.g., jaundice, coagulopathy, abdominal pain).

Participants with underlying active liver disease (see Section 5.2) will be excluded from this study. Participants experiencing hepatic enzyme elevation should be treated and managed per standard of care and protocol guidelines (see Section A4–4.3.1).

A4–1.3 POTENTIAL DRUG INTERACTIONS

Divarasib has been shown to have the potential to induce the messenger RNA (mRNA), but not the protein levels of CYP3A4 in human hepatocyte culture. Therefore, interaction with co-administered CYP3A4 substrates cannot be excluded at this point. As such, care should be taken with co-administered drugs that are metabolized by these enzyme systems, especially if those drugs have a narrow therapeutic index, because their systemic concentrations could be altered when co-administered with divarasib. CYP3A4 may play a role in the metabolism of divarasib, so there is a potential for drug-drug interaction with co-administered CYP3A4 modulators. Thus, caution should be taken with any medication that is metabolized by or strongly inhibits or induces this enzyme (see Section 6.8.2.1).

Divarasib has been shown to inhibit P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters in vitro. While exposure of prototypical substrates of P-gp and BCRP transporters is not predicted to be affected based on physiologically based pharmacokinetic modeling-based simulations in the clinical dose range of divarasib, interaction with co-administered P-gp, and BCRP substrates cannot be excluded. Caution should be taken with any medication that is an exclusive substrate of P-gp or BCRP with a narrow therapeutic index (see Section 6.8.2.1).

A4–2 RISKS ASSOCIATED WITH SOTORASIB

Sotorasib has been associated with hepatotoxicity and interstitial lung disease (ILD)/pneumonitis.

Hepatotoxicity

Sotorasib can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. Sotorasib has been associated with transient elevations of serum transaminases (ALT and AST). These elevations improved or resolved with dose modification or permanent discontinuation of treatment and did not result in any cases of

liver failure or fatal cases in clinical studies. Cases of liver enzyme increase can be asymptomatic. Participants should be monitored for liver function (ALT, AST and total bilirubin) prior to the start of sotorasib, and during treatment with sotorasib, with more frequent testing in participants who develop transaminase and/or bilirubin elevations.

Interstitial Lung Disease (ILD)/pneumonitis

ILD/pneumonitis occurred in patients treated with sotorasib with prior exposure to immunotherapy or radiotherapy and the events can be fatal. Monitor participants for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever).

For more details on the safety profile of sotorasib, refer to the applicable local prescribing information.

A4–3 RISKS ASSOCIATED WITH ADAGRASIB

Adagrasib has been associated with gastrointestinal adverse reactions, QTc interval prolongation, hepatotoxicity, and ILD/pneumonitis.

Gastrointestinal Adverse Reactions

Adagrasib can cause severe gastrointestinal adverse reactions. Monitor and manage participants using supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated.

QTc Interval Prolongation

Adagrasib can cause QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (e.g., torsades de pointes) or sudden death. Adagrasib causes concentration dependent increases in the QTc interval (see Section 6.8.2.3)

Hepatotoxicity

Adagrasib can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. Monitor liver laboratory tests (AST, ALT, alkaline phosphatase and total bilirubin) prior to the start of and during treatment with adagrasib or as clinically indicated, with more frequent testing in participants who develop transaminase elevations.

ILD/Pneumonitis

Adagrasib can cause ILD/pneumonitis, which can be fatal. Monitor participants for new or worsening respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever) during treatment with adagrasib. Withhold adagrasib in participants with suspected ILD/pneumonitis.

Severe Cutaneous Adverse Reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with adagrasib. Patients should be advised of the signs and symptoms and be monitored closely for skin reactions. If a SCAR is suspected, adagrasib should be withheld, and the patient should be referred to a *specialized* unit for assessment and treatment. If SJS, TEN or DRESS related to adagrasib is confirmed, adagrasib should be permanently discontinued.

For more details on the safety profile of adagrasib, refer to the applicable local prescribing information.

A4–4 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

Guidelines for the management of specific adverse events and dose modifications below are intended to inform rather than supersede clinical judgment and the benefit−risk balance as assessed by the investigator in managing individual cases.

For specific adverse events for all IMPs, the following general rules should apply:

- Investigate etiology (see relevant Investigator's Brochure, SmPC, or Prescriber Information for specific guidelines).
- Initiate treatment as per institutional guidelines and check the relevant Investigator's Brochure or SmPC or Prescriber Information for specific management guidelines.
- In general, study treatment should be interrupted for Grade ≥3 adverse events. In case of suspected interstitial lung disease (ILD) / pneumonitis of any grade, please follow the management guideline provided by sotorasib / adagrasib prescriber information to withhold study drug if ILD / pneumonitis is suspected and permanently discontinue study drug if ILD / pneumonitis is confirmed.
- *Corticosteroids may be considered when there is a suspected immune-mediated adverse event, particularly in patients with recent CPI exposure, at the discretion of the investigator, after ruling out infectious or alternative etiology. Early intervention with focus on prioritization of participant safety is recommended, as deemed appropriate by the investigator.*
- Contact the Medical Monitor as appropriate and as per Investigator's Brochure guidance.

A4–4.1 DOSE MODIFICATIONS

The divarasib dose modification instructions provided are intended to serve as recommended guidelines to allow ongoing treatment for participants experiencing clinical benefit without signs or symptoms of progression while monitoring participant safety.

These guidelines are intended to inform rather than supersede clinical judgment and the investigator's assessment of the benefit-risk balance in managing individual cases.

The dose of divarasib can be reduced by one dose level up to two times for management of treatment-related toxicities (i.e., from 400 mg to 200 mg and then from 200 mg to 100 mg). If further dose reduction is indicated after two dose reductions, the participant must discontinue divarasib. The Medical Monitor is available to advise as needed.

Please refer to respective local prescribing information for dose modification guidelines of sotorasib and adagrasib.

A4–4.2 TREATMENT INTERRUPTION

If divarasib has been withheld for $>$ 1 cycle because of toxicity, treatment with divarasib should be discontinued unless the investigator deems resumption of treatment to be in the best interest of the participant based on a benefit-risk assessment. Divarasib treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit-risk by the investigator and documented by the investigator. The Medical Monitor is available to advise as needed.

Please refer to respective local prescribing information for dose interruption guidelines of sotorasib and adagrasib.

A4–4.3 MANAGEMENT GUIDELINES

A4–4.3.1 Management Guidelines for Adverse Events Associated with Divarasib

Guidelines for management of specific adverse events with divarasib are outlined in Table A4-1.

Table A4-1 Guidelines for Management of Adverse Events for Participants Receiving Divarasib

Event	Action to Be Taken
Gastrointestinal Toxicities (Nausea, Vomiting)	
General	• Infectious or alternate etiology should be excluded. • Participants should be closely monitored for GI symptoms and effects on wellbeing. Participants experiencing nausea and/or vomiting should be managed according to local standards of care, including dietary modification, use of anti-emetic agents, and additional supportive care as appropriate (e.g., oral or IV hydration). • Participants should have anti-emetic medication available for use prior to initiation of divarasib (see Section 6.8.1). • Re-escalation of divarasib dose upon clinical improvement is allowed based on the investigator's assessment of benefit-risk. The Medical Monitor is available to advise as needed.
Grade 1 or 2	• Manage with supportive care according to the local standard of care. • If no response is noted with maximum first line therapy after 24–48 hours, consider initiating alternative or second line therapy. • If persistent despite maximum medical therapies, interrupt treatment with divarasib until resolution to Grade $\leq$ 1. Participant may resume divarasib at same dose level.
Grade $\geq$ 3	• Manage with supportive care according to local standard of care. • Interrupt treatment with divarasib until resolution to Grade $\leq$ 1. Consider resuming divarasib at one dose level lower. • Consider consultation with gastroenterologist if inadequate response despite maximum therapy and divarasib interruption. • If Grade 4, permanently discontinue divarasib.

Table A4-1 Guidelines for Management of Adverse Events for Participants Receiving Divarasib

Event	Action to Be Taken
Gastrointestinal Toxicities (Diarrhea)	
General	• Infectious or alternate etiology should be excluded. • Participants should be closely monitored for GI symptoms and effects on wellbeing. Participants experiencing diarrhea should be managed according to local standards of care, including dietary modification, use of antidiarrheal agents, and additional supportive care as appropriate (e.g., oral or IV hydration). • In participants with diarrhea and recent CPI exposure [a]: Consider early consultation with gastroenterologist in addition to assessment for infectious or inflammatory etiology (e.g., CRP, ESR, ferritin). • Dietary modifications: Stop all lactose-containing products and eat small meals. The BRAT (banana, rice, apples, toast) diet may be helpful. Encourage adequate hydration. • Participants should have anti-diarrheal medications available for use prior to initiation of divarasib (see Section 6.8.1). • Re-escalation of divarasib is allowed upon clinical improvement based on the investigator's assessment of benefit-risk. The Medical Monitor is available to advise as needed.
Grade 1 or 2	• Manage with supportive care according to the local standard of care. • If inadequate response with maximum first line therapy after 24–48 hours, consider initiating alternative or second line therapy. • If persistent despite maximum medical therapies, interrupt treatment with divarasib until resolution to Grade ≤ 1. Participant may resume divarasib at same dose level. • In participants with recent CPI exposure [a]: Consider consultation with gastroenterologist if persistent diarrhea despite maximum medical therapy.
Grade ≥ 3	• Manage with supportive care according to local standard of care. • Interrupt treatment with divarasib until resolution to Grade ≤ 1. • Consider consultation with gastroenterologist if inadequate response despite maximum therapy and divarasib interruption. • In participants with recent CPI exposure [a]: early consultation with gastroenterologist with endoscopy and biopsy is encouraged. • Participants may resume divarasib at one dose level lower when diarrhea improves to Grade ≤ 1. • If Grade 4, permanently discontinue divarasib.

Table A4-1 Guidelines for Management of Adverse Events for Participants Receiving Divarasib

Event	Action to Be Taken
Elevation of Hepatic Transaminases	
General	• Participants presenting with jaundice, coagulopathy, abdominal pain or other symptoms suggestive of hepatic pathology should have liver function tests checked and imaging of the liver performed. If liver enzymes are elevated with no obvious malignant cause, a hepatologist should be consulted. • Participants experiencing hepatic enzyme elevation should be treated and managed according to local standard of care. • In participants with recent CPI exposure [a]: consider early consultation with a hepatologist and corticosteroid [b] treatment after ruling out infectious or alternative etiology.
Grade 1 or 2	• Consider more frequent monitoring until Grade ≤ 1. • In participants with recent CPI exposure [a]: consider consultation with hepatologist and oral corticosteroid [b] treatment after ruling out infectious or alternative etiology.
Grade ≥ 3	• Interrupt treatment with divarasib until resolution to Grade ≤ 1. Consider resuming divarasib at one dose level lower. • In participants with recent CPI exposure [a]: consultation with a hepatologist is encouraged. Corticosteroid [b] treatment with slow taper after ruling out infectious or alternative etiology. • If Grade 4 or any case meeting Hy's Law criteria, permanently discontinue divarasib.

C1D1 = Cycle 1, Day 1; CPI = checkpoint inhibitor; GI = gastrointestinal.

[a] Defined as the last administered dose of CPI < 3 half-lives from C1D1 of divarasib.

[b] For Grade 1 or 2 toxicities, consider prednisone 10–20 mg QD or equivalent dose of alternative corticosteroid. For Grade 3 toxicities, consider prednisone 60 mg QD or 1 mg/kg or equivalent dose of alternative corticosteroid as deemed clinically appropriate by the investigator.

A4–4.3.2 Management Guidelines for Adverse Events Associated with Sotorasib or Adagrasib

Refer to the local sotorasib or adagrasib prescribing information and institutional guidelines for details on management of adverse events associated with sotorasib or adagrasib.

A4–4.4 MANAGEMENT OF INCREASES IN QT INTERVAL

Divarasib should be discontinued in participants who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements >30 minutes apart) QT interval corrected through use of Fridericia's formula (QTcF) that is >500 ms and >60 ms longer than the baseline value

- Sustained absolute QTcF that is $>$515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of participants with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such participants.

In rare circumstances, it may be acceptable to resume divarasib, at a lower dose, provided any ECG abnormalities have resolved and the participant is appropriately monitored. Clinical judgment should be applied.

Appendix 5
Collection of Pregnancy Information

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A5–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 7 days after the final dose of sotorasib, 5 days after the final dose of adagrasib, or divarasib. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Sharing of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A5–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within $5\ days$ after the final dose of divarasib. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Sharing of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional

information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Sharing of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A5–3 ABORTIONS

A spontaneous abortion in a female participant exposed to study treatment or the female partner of a male participant exposed to divarasib should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A5–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to divarasib should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 6
Clinical Outcome Assessment Instruments

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A6–1 CLINICAL OUTCOME ASSESSMENT INSTRUMENTS

PRO instruments will be self-administered or interviewer-administered at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3). PRO instruments may be completed at home during the follow-up period as needed (see schedule of activities in Section 1.3). At the clinic, instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and *ideally* prior to the administration of study treatment. In scenarios where the non-PRO assessments (e.g., blood draws, imaging scans) are completed at a different location than the one providing treatment or are performed on a different day *or time* than study treatment administration, the non-PRO assessments can be completed before the completion of PRO questionnaires as long as the results have not been discussed with participants. *Considering the study medication is taken orally on a daily basis, and the participant has been instructed to take the medication at approximately the same time each day, it is possible that the PROs will be completed after drug administration. This is acceptable in these situations. On days when the participant is coming to clinic, in the event participants are instructed to hold treatment until after the visit, the PROs should be completed prior to treatment administration; however, it is acceptable if they have not held treatment.*

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

Participants should be given the following instructions for completing PRO instruments at home:

- Participants should complete the instruments in a quiet area with minimal distractions and disruptions.
- Participants should answer questions to the best of their ability; there are no right or wrong answers.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During clinic visits, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.

- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be 24 minutes at each specified visit during the study treatment period and 15 minutes at each specified visit during the follow-up period.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

A6–1.1 EORTC QLQ-C30

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Specimen

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Specimen

A6–1.2 EORTC QLQ-LC13

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ENGLISH



EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

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A6–1.3 NCI PRO-CTCAE

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NCI PRO-CTCAE ™ ITEMS
Item Library Version 1.0
English
Form Created on 01 December 2021

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
2b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

SPECIMEN

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.

6a. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
6b. In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

7a. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7b. In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8a. In the last 7 days, did you have any RASH?	
O Yes	O No

9a. In the last 7 days, what was the SEVERITY of your ACNE OR PIMPLES ON THE FACE OR CHEST at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

10a. In the last 7 days, did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

11a. In the last 7 days, how OFTEN did you have a HEADACHE?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
11b. In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
11c. In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

12a. In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
12b. In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
12c. In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

SPECIMEN

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A6–1.4 EORTC IL46

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ENGLISH

EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

SPECIMEN

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A6–1.5 EUROQOL EQ-5D-5L

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Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g., work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

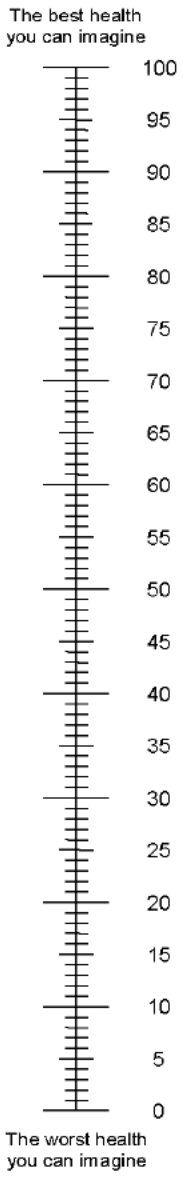
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Appendix 7
Genetics: Use and Analysis of DNA for Mandatory Samples

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to divarasib and non–small cell lung cancer (NSCLC) and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to divarasib and treatments of this drug class and NSCLC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

DNA samples will be analyzed for germline and/or somatic variants. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to divarasib or study treatments of this class to understand the study disease or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

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

The samples will be retained while research on divarasib and treatments of this drug class or NSCLC continues but no longer than the period approved as per local requirements.

Appendix 8
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.
- *Patients with only one potential target lesion located in a previously irradiated area are generally not considered eligible for the study.*

METHODS FOR ASSESSING LESIONS

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is $\leq$ 5 mm. When CT scans have slice thickness of $>$ 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new

lesions on a different modality, because the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

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

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

axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should

be assigned in this circumstance as well, and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedules of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A8-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A8-1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all 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.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

having "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A8-1.

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

REFERENCES

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

Appendix 9
Drugs Known to Increase QT Interval

The following table is a sample list of drugs known to increase QT interval. This list is not exhaustive and the full list is provided in Woosley et al.

Aripiprazole	Flupentixol	Perphenazine
Artenimol + piperaquine	Gemifloxacin	Pilsicainide
Asenapine	Hydrocodone - ER	Pipamperone
Atomoxetine	Granisetron	Promethazine
Bedaquiline	Imipramine	Prothipendyl
Bendamustine	Isradipine	Rilpivirine
Bortezomib	Ketanserin	Risperidone
Bosutinib	Lapatinib	Romidepsin
Buprenorphine	Lenvatinib	Saquinavir
Capecitabine	Leuprolide	Sertindole
Ceritinib	Lithium	Sorafenib
Clomipramine	Melperone	Tacrolimus
Clozapine	Mifepristone	Tamoxifen
Crizotinib	Mirabegron	Telavancin
Cyamemazine (cyamepromazine)	Mirtazapine	Telithromycin
Dabrafenib	Moexipril/HCTZ	Tetrabenazine
Dasatinib	Nicardipine	Tiapride
Degarelix	Nilotinib	Tizanidine
Delamanid	Norfloxacin	Tolterodine
Desipramine	Nortriptyline	Toremifene
Dexmedetomidine	Ofloxacin	Trimipramine
Dolasetron	Osimertinib	Tropisetron
Efavirenz	Oxytocin	Vardenafil
Eribulin mesylate	Paliperidone	Vemurafenib
Ezogabine (Retigabine)	Panobinostat	Venlafaxine
Famotidine	Pasireotide	Vorinostat
Felbamate	Pazopanib	Zotepine
Fingolimod	Perflutren lipid microspheres	

REFERENCE

Woosley RL, Heise CW, Gallo T, et al. QTdrugs List [resource on the internet]. 2023 [cited 22 January 2024]. Available from: https://crediblemeds.org/healthcare-providers/clinical-overview-long-qttorsades.

Appendix 10
Investigational, Non-Investigational, and Auxiliary Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A10-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for the European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in the EEA	Used within Marketing Authorization
Divarasib (RO7435846)	IMP (test product)	Unauthorized	Not applicable
Sotorasib	IMP (comparator)	Authorized	Yes
Adagrasib	IMP (comparator)	Authorized	Yes

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.

Table A10-2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in the UK	Used within Marketing Authorization
Divarasib (RO7435846)	IMP (test product)	Unauthorized	Not applicable
Sotorasib	IMP (comparator)	Authorized	Yes
Adagrasib	IMP (comparator)	Authorized	Yes

IMP = investigational medicinal product; NIMP = non-investigational medicinal product; UK = United Kingdom.

Appendix 11
Abbreviations

Abbreviation or Term	Definition
BCRP	breast cancer resistance protein
BEN	benign ethnic neutropenia
BICR	blinded independent central review
BID	twice daily
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CT	computed tomography
DDI	drug-drug interaction
DOR	duration of response
EBUS	endobronchial ultrasound
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
F1LCDx	FoundationOne® Liquid CDx assay
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GHS	global health status
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IL46	(EORTC) Item List 46
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	independent review facility
KEAP1	Kelch-like ECH-associated protein 1
KRAS G12C	Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine
KRAS G12C +	*KRAS G12C*-positive
LPLV	last participant, last visit

Appendix 11: Abbreviations

Abbreviation or Term	Definition
MN	mobile nursing
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetic
PO	orally; by mouth
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	PRO Common Terminology Criteria for Adverse Events
QD	once daily
QoL	quality of life
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
TTCD	time to confirmed deterioration
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

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Approval Task	[redacted] Company Signatory 11-Oct-2025 03:58:23 GMT+0000

PROTOCOL, VERSION 2:
RATIONALE

Protocol BO45217 Version 2 has been created separate from the global protocol to reflect updates requested from the European health authorities as part of the EU CTR submission. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The Schedule of Activities (Table 1) has been modified to allow for some procedures to be performed during an optional pre-screening visit where convenient, for more flexibility for the participants (Section 1.3).
- The Schedule of Blood-Based Pharmacokinetic and Biomarker Samples has been updated to include plasma for safety biomarkers at treatment discontinuation and as clinically indicated (Section 1.3).
- The option for study participants to consider mobile nursing has been updated to clarify that it is not applicable to participants in the European Economic Area (Sections 1.3 and 8).
- The primary endpoint of the study has been updated to progression free survival (PFS) by blinded independent central review (BICR) to align with Health Authority and Ethics Committee requests (Sections 1.3, 3.1, 9).
- The study design has been updated to provide details on the potential for supply limitations of the control drugs, and how the Sponsor and Investigators will navigate these scenarios if they were to arise (Section 4.1).
- The Inclusion Criteria regarding lung cancer status has been updated to remove specific AJCC staging, as this is less relevant for patients who have received prior treatment for advanced/metastatic disease. The key criteria were retained and specify patients must have disease that is unresectable and not amenable to treatment with combined chemoradiation (Section 5.1).
- The contraception requirements for divarasib have been updated to state that participants must remain abstinent or use two methods of contraception for 5 days after the final dose of divarasib. This change is based on the end of relevant systemic exposure of divarasib, and on updated results from negative genotoxic and embryo-fetal toxicity pre-clinical studies (Section 5.1).
- The protocol has been updated in various sections to align with the adagrasib Summary of Product Characteristics as it pertains to contraception requirements after discontinuing treatment with adagrasib (Sections 5.1, Appendices 3 and 4).
- The secondary objectives have been updated to consider objective response rate (ORR) as a key secondary endpoint. ORR will also be assessed for this endpoint according to BICR as opposed to investigator (Sections 3.1 and 9.3.3.2).
- Text has been updated to add two additional strengths of sotorasib (240 mg and 320 mg), as these strengths are approved or available in some of the countries participating in the trial (Section 6.1).

- Text has been updated to remove the guidance to take divarasib with a minimum of 240 mL of water to reflect the information in the most updated Investigator's Brochure (Section 6.1.1).
- Text has been updated to align with the Sotorasib SmPC regarding how to handle missed doses (Section 6.1.2).
- Dexamethasone has been added to the list of anti-emetics that may be administered before initial treatment with study drugs (Section 6.8.1).
- Language has been added to specify that patients who are being screened for the study should discontinue herbal therapies prior to study treatment initiation, and that for patients enrolled in the study previously who are taking herbal therapies, a risk-benefit assessment should be performed by the investigator. This has been added to reinforce the uncertainty of safety and drug interaction potential posed by herbal therapies (Section 6.8.2.4).
- The study assessments have been updated to specify that the results of any molecular testing for genes or proteins of interest will be collected (Section 8).
- The degree of exposure to brain imaging assessments in the study compared with standard of care treatment has been clarified (Section 8.1).
- The potential analysis of 2-hour post-dose concentration of adagrasib and sotorasib has been removed (Section 8.4).
- Sample requirements were changed for the optional disease progression biopsy to allow for the collection of both formalin-fixed, paraffin-embedded and fresh frozen tissue samples to enable single cell analysis and/or establish patient-derived xenograft (PDX) models (Sections 1.3 and 8.10.2).
- Text has been added to include ORR in the formal hierarchical testing procedure (Section 9.1).
- Text has been added to clarify that a sensitivity analysis will be performed for PFS as determined by the investigator (Section 9.3.2).
- A table has been added to clarify the timeline and mechanism for collecting and reporting adverse events (Appendix 3).
- Language has been added to provide more specific management information for participants who develop interstitial lung disease (ILD) (Appendix 4).
- Text has been added to clarify that serious adverse events should always be reported, even when not severe or possibly unrelated to study treatment (Appendix 3).
- Risks associated with adagrasib have been updated to include Severe Cutaneous Adverse Reactions (SCAR) in accordance with the adagrasib Summary of Product Characteristics (Appendix 4).
- General rules on how to manage participants who experience adverse events have been added for clarify (Appendix 4).
- The adverse events of special interest (AESIs), potential risks, and safety management guidelines for divarasib have been updated to remove

stomatitis/mucosal inflammation as it is no longer considered an AESI for divarasib (Appendix 4).

Additional minor changes have been made to improve clarity and consistency. Appropriate updates have also been made to the appendices. Substantive new information appears in italics.

PROTOCOL, VERSION 3:
RATIONALE

Protocol BO45217 Version 3 has been updated primarily to incorporate the changes from a global protocol clarification letter issued to sites, to revise a key secondary endpoint to 'confirmed objective response', and to align the safety-related updates with the most updated divarasib Investigator's Brochure.

Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- A key secondary endpoint, objective response rate, has been updated to 'confirmed objective response', defined as a complete response or partial response on two occasions ≥ 4 weeks to prevent overestimation of the observed response rate. Duration of response will also be assessed using confirmed objective response (Sections 1.1, 3.2, and 9).
- Text has been added to clarify that both total and direct bilirubin may be performed as a part of the chemistry panel at each visit; however, only total bilirubin is required if results are within normal range. If total bilirubin is out of range, then direct bilirubin must also be performed, as it is clinically indicated to further evaluate the abnormal finding (Section 1.3, Appendix 2).
- Schedule of activities has been updated to clarify that Patient-Reported Outcome (PRO) assessments are required only at Months 3 and 6 post-treatment discontinuation to align the timing of PRO collection with the study treatment dosing schedule (Section 1.3).
- Text has been updated to clarify that all screening assessments may be performed within 48 hours prior to Cycle 1 Day 1 and do not need to be repeated on Day 1 of Cycle 1 (Section 1.3).
- Language has been added to clarify biomarker collection during unscheduled visits and to specify requirements for biomarker sampling when treatment is interrupted at a given visit (Section 1.3).
- Guidance on timing of PROs was updated to clarify that PROs may be completed after dosing or other assessments, provided the participant has not received feedback from those assessments (Section 1.3, Appendix 6).
- Text has been updated to clarify that testing for known concomitant second oncogenic driver mutations is not required to determine eligibility, unless required by local authorities (Section 5.2).
- Text has been updated to recommend taking divarasib with sufficient water to aid swallowing, based on the in vitro data demonstrating that divarasib adipate salt has high aqueous solubility (see IBv7 section 1.2). The volume of water intake with divarasib tablet is not predicted to impact the extent of drug absorption (Section 6.1.1).

- Amlodipine and manidipine have been added as examples of CYP3A4 substrates with narrow therapeutic indices that should be avoided when co-administered with sotorasib in accordance with the sotorasib Summary of Product Characteristics (Section 6.8.2.2).
- The following have been removed since it is not reflective of current practices (Section 8.3.4).
- Requirement to file safety reports with the IB.
- Sponsor comparison of the frequency of event severity.
- The adverse events of special interest (AESIs) for divarasib have been updated to remove stomatitis/mucosal inflammation as it is no longer considered an AESI for divarasib (Section 8.3.8).
- The text has been updated to clarify that tumor tissue from bone is not acceptable (Section 8.7).
- The Sponsor's policy on trade secrets has been described in Section A1-10 to increase transparency (Section A1-10).
- The timeline and mechanism for collecting and reporting adverse events has been clarified in Table A3-1 to align with other sections of the protocol and to ensure consistent AE reporting (Appendix 3).
- Removed the word 'potential' from the gastrointestinal toxicities and elevation of hepatic transaminases risks associated with divarasib as these risks are now referred to as 'identified risks' as per the most updated Investigator’s Brochure (Appendix 4).
- General rules on how to manage participants who experience suspected immune-mediated adverse events with corticosteroids have been added for clarity (Appendix 4).
- The pregnancy reporting period for female partners of male participants was clarified to 5 days to align with the latest Investigator’s Brochure and other protocol sections (Appendix 5).
- Text was added to clarify that patients with only one potential target lesion in a previously irradiated area may be considered ineligible (Appendix 8).

Additional minor changes have been made to improve clarity and consistency. Appropriate updates have also been made to the appendices. Substantive new information appears in italics.

STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF DIVARASIB VERSUS SOTORASIB OR ADAGRASIB IN PATIENTS WITH PREVIOUSLY TREATED *KRAS G12C*-POSITIVE ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER**
STUDY NUMBER:	BO45217
STUDY NAME:	Krascendo 1
VERSION NUMBER:	1
ROCHE COMPOUND(S):	Divarasib (RO7435846)
EU CT NUMBER:	2024-510908-37-00
IND NUMBER:	147339
NCT NUMBER:	NCT06497556
PLAN PREPARED BY:	[redacted], Msc

STATISTICAL ANALYSIS PLAN APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 3.0.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	Adverse event
AESI	Adverse events of special interest
BICR	Blinded independent central review
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full analysis set
FDA	Food and Drug Agency
ICH	International Council on Harmonization
iDMC	Independent Data Monitoring Committee
IRF	Independent review facility
IxRS	Interactive Voice/Web-Based Response System
KEAP1	Kelch-like ECH-associated protein 1
KRAS G12C	Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine
NCI	National Cancer Institute
NGS	Next-generation sequencing
NPT	Non-protocol specified anticancer therapy
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PD-L1	Programmed death-ligand 1
PFS	Progression-Free Survival
PRO	Patient-Reported Outcomes
PD	Progressive disease
PK	Pharmacokinetic
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TTCD	Time to confirmed deterioration
ULN	Upper limit of normal

1. INTRODUCTION

The analyses described in this Statistical Analysis Plan (SAP) will supersede those specified in Protocol BO45217 for the purposes of a regulatory filing. The purpose of this study is to assess the efficacy and safety of divarasib, a Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine (KRAS G12C) inhibitor, compared to locally approved KRAS G12C inhibitors (sotorasib or adagrasib) in patients with KRAS G12C−positive (KRAS G12C+) advanced or metastatic non-small cell lung cancer (NSCLC) who have been previously treated with standard of care treatments in the advanced or metastatic setting.

There are no changes to the planned analyses described in the protocol.

1.1 TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS

The primary and key secondary objectives for the study are expressed using the estimand framework in accordance with the International Council on Harmonization (ICH) E9(R1) statistical principles for clinical trials (ICH 2020). Other secondary as well as exploratory objectives and corresponding endpoints are described below in Table 1.

Table 1 Trial Objectives, Endpoints and Estimands

Primary Objective	Estimand Definition

To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: Individuals with KRAS G12C+ advanced or metastatic NSCLC who have received at least one prior systemic therapy
	• Endpoint: progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression, as determined by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause (whichever occurs first)
	• Treatment:
	  ○ Experimental arm: divarasib 400 mg once a day (QD)
	  ○ Control arm: KRAS G12C inhibitor (sotorasib 960 mg QD or adagrasib 600 mg twice daily [BID]), depending on investigator's choice, as applicable
	• Intercurrent events and handling strategies:
	  ○ Early discontinuation from study treatment: treatment policy strategy
	  ○ Start of non-protocol specified anticancer therapy prior to disease progression: treatment policy strategy
	• Population-level summary: hazard ratio for PFS

Key Secondary Objectives	Estimand Definitions

To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: as defined above for PFS
	• Endpoint: overall survival (OS), defined as the time from randomization to death from any cause
	• Treatment: as defined above for PFS
	• Intercurrent events and handling strategies:
	  ○ Early discontinuation from study treatment: treatment policy strategy
	  ○ Start of non-protocol specified anticancer therapy: treatment policy strategy
	• Population-level summary: hazard ratio for OS

To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: as defined above for PFS
	• Endpoint: confirmed objective response, defined as complete response or partial response on two occasions $\geq$ 4 weeks apart, as determined by BICR according to RECIST v1.1
	• Treatment: as defined above for PFS
	• Intercurrent events and handling strategies:
	  ○ Early discontinuation from study treatment: composite variable strategy
	  ○ Start of non-protocol specified anticancer therapy prior to best overall response: composite variable strategy
	• Population-level summary: difference between treatment arms in the proportion of individuals achieving confirmed objective response

To evaluate, from the participant's perspective, the functioning and impact of key disease-related symptoms of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Population: as defined above for PFS
	• Endpoint: time to confirmed deterioration (TTCD) on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 dyspnea item and the physical functioning scale, and the cough scale of the QLQ-LC13 scales; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death
	• Treatment: as defined above for PFS
	• Intercurrent events and handling strategies:
	  ○ Early discontinuation from study treatment prior to a confirmed clinically meaningful deterioration: treatment policy strategy
	  ○ Start of non-protocol specified anticancer therapy prior to a confirmed clinically meaningful deterioration: hypothetical strategy

	○ Death that occurs before participants report any clinically meaningful deterioration: while-alive strategy • Population-level summary: hazard ratio for TTCD
Other Secondary Objectives	**Corresponding Endpoints**
To evaluate the efficacy of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Duration of response (DOR), defined as the time from the first occurrence of a documented confirmed objective response to disease progression, as determined by BICR according to RECIST v1.1, or death from any cause (whichever occurs first)
To evaluate the safety and tolerability of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Incidence and severity of adverse events, with severity determined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grading scale • Change from baseline in selected vital signs and electrocardiogram (ECG) parameters • Change from baseline in selected clinical laboratory test results • Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne) as assessed through use of the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) • Change from baseline in diarrhea, nausea, vomiting, anorexia, alopecia, dyspnea, cough, constipation, myalgia, headache, and rash/acne as assessed through use of the NCI PRO-CTCAE • Frequency of participants' response of the degree they are troubled with treatment symptoms, as assessed through use of the single-item EORTC Item List (IL46)
To evaluate the quality of life (QoL) of participants treated with divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Change from baseline in cough, chest pain, dyspnea, physical and role functioning, and global health status (GHS)/QoL at each timepoint as assessed through use of the EORTC QLQ-LC13 and QLQ-C30 • TTCD on the EORTC QLQ-C30 role functioning and GHS/QoL scales and the chest pain scale of the QLQ-LC13; TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death

Exploratory Objectives	Corresponding Endpoints
To assess the central nervous system (CNS) activity of divarasib compared with KRAS G12C inhibitors (sotorasib or adagrasib)	• Cumulative incidence rates of CNS progression as determined by BICR according to RECIST v1.1, at 6 and 12 months • Time to CNS progression as determined by BICR according to RECIST v1.1, defined as the time from randomization until first radiographic evidence of CNS progression • Intracranial PFS as determined by BICR according to RECIST v1.1, defined as the time from randomization until first radiographic evidence of CNS progression or death from any cause (whichever occurs first)
To characterize pharmacokinetics (PK) of divarasib	• Plasma concentration of divarasib at specified timepoints
To characterize PK of sotorasib	• Plasma concentration of sotorasib at specified timepoints
To characterize PK of adagrasib	• Plasma concentration of adagrasib at specified timepoints
To evaluate potential relationships between drug exposure and the efficacy and safety of divarasib	• Relationship between plasma concentration or PK parameters for divarasib and efficacy endpoints • Relationship between plasma concentration or PK parameters for divarasib and safety endpoints
To evaluate potential relationships between selected covariates and exposure to divarasib	• Relationship between selected covariates and plasma concentration or PK parameters for divarasib

To identify and/or evaluate biomarkers that are predictive of response to divarasib compared with KRAS G12C inhibitors (sotorasib and adagrasib) (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to divarasib compared with KRAS G12C inhibitors, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of divarasib activity (i.e., pharmacodynamic biomarkers) compared with KRAS G12C inhibitors, or can increase the knowledge and understanding of disease biology and drug safety or pharmacokinetics	• Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, or other biomarker endpoints
To evaluate and compare participants' health status to generate utility scores for use in economic models for reimbursement	• Health status, as assessed by the EuroQol EQ-5D-5L questionnaire

BICR = blinded independent central review; BID = twice daily; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of response; ECG = electrocardiogram; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; KRAS G12C = Kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; QD = once a day; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TTCD = time to confirmed deterioration.

1.2 STUDY DESIGN

This is a Phase III, randomized, active control, open-label study evaluating the efficacy and safety of divarasib versus KRAS G12C inhibitors, sotorasib or adagrasib, in patients with previously treated KRAS G12C+ advanced or metastatic NSCLC.

The study includes a screening period of up to 28 days, a treatment period, and a long-term follow-up period for progression-free survival (PFS) and overall survival (OS). The total duration of study participation for each individual is expected to range from 1 day to more than 4 years.

The primary analysis will be conducted when the required number of events is collected for the analysis of the primary endpoint PFS (see Section 2.2). The final OS analysis will be conducted when the required number of events is collected for OS (see Section 2.2).

1.2.1 Treatment Assignment

This is a randomized, open-label study.

Participants will be randomly assigned to one of two treatment arms: divarasib or locally approved KRAS G12C inhibitor (sotorasib or adagrasib). In countries where both sotorasib and adagrasib are approved, investigators will have a choice between the two therapies. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm.

Randomization will be stratified by Kelch-like ECH-associated protein 1 (KEAP1) mutation status (mutation detected or not detected/unknown) determined by the Sponsor's designated testing laboratory or preexisting results from Sponsor-approved tests, history of central nervous system (CNS) metastasis (yes or no), and intended KRAS G12C inhibitor in the control arm (sotorasib or adagrasib). Unknown results for KEAP1 are not allowed for preexisting next-generation sequencing (NGS) tests.

1.2.2 Independent Review Facility

Imaging data used for tumor assessments by the investigator will be collected to enable a blinded independent central review (BICR) of response endpoints. An independent review facility (IRF) will review all available (de-identified) radiographic tumor assessments to assess tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Details of the IRF's responsibilities and procedures will be specified in a separate IRF charter.

1.2.3 Data Monitoring

An independent Data Monitoring Committee (iDMC) will be established to conduct periodic reviews of aggregate safety data. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the frequency of the reviews, the summary of the data, and their roles and responsibilities.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The purpose of this study is hypothesis testing, testing superiority of divarasib compared with the locally approved KRAS G12C inhibitors with respect to PFS. The null (H_0) and alternative (H_1) hypotheses for the primary endpoint PFS in the Full Analysis Set (FAS)

will be tested at a two-sided significance level of 0.05 and can be phrased in terms of the population hazard ratio (HR) λ between the experimental arm and the control arm:

$$H_0: \lambda = 1 \text{ versus } H_1: \lambda \neq 1$$

Null and alternative hypotheses of a similar form will be tested for the key secondary endpoints OS and time to confirmed deterioration (TTCD).

For confirmed objective response rate (ORR), the following null (H_0) and alternative (H_1) hypotheses will be tested at a significance level of 0.05:

$$H_0: p_{\text{experimental}} = p_{\text{control}} \text{ versus } H_1: p_{\text{experimental}} \neq p_{\text{control}}$$

where $p_{\text{experimental}}$ and p_{control} refer to the proportion of participants with a confirmed objective response in the experimental and the control arms, respectively.

All hypothesis tests will be two-sided unless stated otherwise.

2.2 SAMPLE SIZE DETERMINATION

A total of approximately 320 participants will be enrolled in this study and randomized in a 1:1 ratio to either divarasib or locally approved KRAS G12C inhibitor (sotorasib or adagrasib). The sample size is determined by the primary endpoint, PFS, and the key secondary endpoint, OS.

Methods of adjusting for multiplicity due to multiple endpoints in order to preserve the Type I error are described below (Section 2.2.1).

The enrollment is projected to complete approximately 14 months after randomization of the first participant with a peak recruitment rate of 32 participants per month. An annual dropout rate of 10% for both arms is assumed. On that basis, it is projected that the primary PFS analysis will occur approximately 24 months after randomization of the first participant and that the final OS analysis will occur approximately 47 months after randomization of the first participant.

The estimates of the number of events required to demonstrate efficacy with regards to PFS are based on the following assumptions:

- Two-sided significance level of 0.05
- 90% power to detect a hazard ratio of 0.64, corresponding to an improvement in median PFS from 7 months to 10.9 months
- The primary analysis of PFS will be conducted when approximately 216 PFS events are observed
- Under these assumptions, the minimal detectable difference will be a hazard ratio of 0.766 corresponding to an improvement in median PFS from 7 months to approximately 9.1 months

The estimates of the number of events required to demonstrate efficacy with regard to OS are based on the following assumptions:

- Two-sided significance level of 0.05
- 80% power to detect a hazard ratio of 0.69, corresponding to an improvement in median OS from 13 months to 18.8 months
- One interim analysis for OS at the time of the primary PFS analysis (when approximately 66% of the total OS events have occurred), with use of the Lan-DeMets approximation to the O'Brien-Fleming boundaries (for details see Section 4.7)
- The final OS analysis will be conducted when approximately 231 OS events are observed
- Under these assumptions, the minimal detectable difference at the final OS analysis will be a hazard ratio of 0.769 corresponding to an improvement in median OS from 13 months to approximately 16.9 months

The assumptions for median PFS and median OS in the control arm used for sample size calculation are derived from the Phase II studies CodeBreak 100 (median PFS: 6.8 months, median OS: 12.5 months; Skoulidis et al. 2021) and KRYSTAL-1 (median PFS: 6.5 months, median OS: 12.6 months; Jänne et al. 2022). In a conservative approach, given that CodeBreak 100 and KRYSTAL-1 are single arm Phase II studies, median PFS and median OS for the shared control arm in study BO45217 are assumed to be slightly higher than results observed for the individual drugs (sotorasib and adagrasib).

2.2.1 Type I Error Control

To control the overall level of significance at a two-sided error rate of 0.05, comparisons with respect to PFS, OS, confirmed ORR, and TTCD will be conducted hierarchically as follows:

- The primary endpoint PFS will be tested first at an overall two-sided α level of 0.05. If the two-sided p-value corresponding to the stratified log-rank test is less than 0.05, the null hypothesis will be rejected, and it will be concluded that divarasib prolongs duration of PFS relative to sotorasib and adagrasib.
- If divarasib significantly prolongs PFS, then OS will be tested at an overall two-sided α level of 0.05. One interim OS analysis will be performed at the time of the primary PFS analysis. Stopping boundaries for interim and final OS analyses are provided in Section 4.7.

  If divarasib has no significant effect on PFS, then OS will not be tested.
- If divarasib significantly prolongs OS, then confirmed ORR will be tested at an overall two-sided α level of 0.05.

  If divarasib has no significant effect on OS, then confirmed ORR will not be tested.

- If divarasib significantly improves confirmed ORR, then TTCD will be tested at an overall two-sided α level of 0.05 for selected scales in the following hierarchical order (each scale tested only if preceding scale was tested statistically significant):
  - Cough (European Organisation for Research and Treatment of Cancer [EORTC] QLQ-LC13)
  - Dyspnea (EORTC QLQ-C30)
  - Physical functioning (QLQ-C30)

    For each scale, if the two-sided p-value corresponding to the stratified log-rank test is less than 0.05, the null hypothesis will be rejected, and it will be concluded that divarasib prolongs duration of TTCD relative to sotorasib and adagrasib for this scale.

    If divarasib has no significant effect on confirmed ORR, then TTCD will not be tested.

The formal testing for confirmed ORR and TTCD will be performed once statistical significance is reached for OS (at the time of interim or final OS analysis), based on the data from the primary PFS snapshot.

3. ANALYSIS SETS

The analysis sets for the purposes of analyses are defined in Table 2 below.

Table 2 Analysis Sets

Analysis Set	Description
Full analysis set (FAS)	All randomized participants; participants will be included in the analyses according to the treatment to which they were assigned.
Safety analysis set	All participants exposed to study treatment; participants will be analyzed according to the treatment that they actually received.
Response-evaluable set (BICR)	All participants in the full analysis set with measurable disease at baseline according to BICR assessment; participants will be included in the analyses according to the treatment to which they were assigned.
Response-evaluable set (INV)	All participants in the full analysis set with measurable disease at baseline according to investigator assessment; participants will be included in the analyses according to the treatment to which they were assigned.
Pharmacokinetic (PK)-evaluable set	All participants who received at least one dose of study drug and had at least one post-baseline quantifiable PK sample available; participants will be included in the analyses according to the treatment that they actually received.

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

The efficacy analyses will be performed in the FAS, unless otherwise stated, with participants grouped according to the treatment arm to which they were assigned. Also analyses for patient reported outcomes (PRO) data will be performed in the FAS, unless otherwise stated.

Safety and tolerability analyses will be performed on the safety analysis set, with participants grouped according to the treatment that they actually received.

Unless otherwise stated, baseline data are the last data obtained prior to initiation of study treatment.

Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

Throughout the statistical analysis, two-sided tests will be performed at a significance level of 5%, unless otherwise stated. A testing hierarchy will be used to control the overall type I error rate at 5% as specified in Section 2.2.1. All other p-values and 95% confidence intervals will be given in an exploratory manner.

PRO data will be summarized for the scheduled visits. No visit windowing will be applied. That is, for each scheduled visit, only the PRO data collected on the planned visits according to protocol schedule of assessments will be included for the summary analysis. PRO data collected on other dates are counted as “unscheduled” and will not be included in the summary analysis by visit.

4.2 PRIMARY ESTIMAND ANALYSIS

The primary objective of study BO45217 is to evaluate the efficacy of divarasib compared with KRAS G12C inhibitors. The primary efficacy endpoint is PFS, as determined by BICR.

4.2.1 Definition of Primary Endpoint/Estimand

The attributes describing the estimand related to the primary analysis are summarized in Section 1.1. The primary endpoint is PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by BICR according to RECIST v1.1, or death from any cause (whichever occurs first). PFS will be analyzed on the FAS.

Data for participants without the occurrence of disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment. Data

for participants with no tumor assessment performed after the baseline visit will be censored at the time of randomization plus 1 day.

For both intercurrent events, a treatment policy strategy will be applied, i.e., PFS will be assessed irrespective of whether a participant discontinued early from study drug or started non-protocol anticancer therapy prior to disease progression. Tumor assessments will be performed as per the schedule of assessments until disease progression or death, irrespective of the occurrence of any of the intercurrent events.

4.2.2 Main Analytical Approach for Primary Estimand/Endpoint

The primary comparison of interest is the stratified log-rank test (two-sided at 5% significance level) for PFS. The stratification factors are the randomization factors, i.e. KEAP1 mutation status (mutation detected or not detected/unknown), history of CNS metastasis (yes or no) and intended KRAS G12C inhibitor in the control arm (sotorasib or adagrasib), as recorded in the interactive voice/web-based response system (IxRS). Results from an unstratified log-rank test will also be presented.

The hazard ratio for PFS will be estimated using a stratified Cox regression model in order to provide an estimate of the treatment effect. A 95% confidence interval for the hazard ratio will be provided.

The Kaplan-Meier method will be used to estimate the median PFS for each arm with 95% confidence limits, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment arms. The Brookmeyer-Crowley method will be used to construct the 95% confidence interval for the median PFS (Brookmeyer and Crowley 1982).

In addition, for descriptive purposes, the PFS rates at 6, 12 and 18 months will also be estimated by using the Kaplan-Meier method for each treatment arm and the 95% confidence intervals calculated by using the standard error derived from Greenwood's formula.

4.2.3 Sensitivity Analyses

4.2.3.1 Investigator-assessed PFS

PFS as determined by the investigators per RECIST v1.1 will be analyzed as described for BICR-assessed PFS in Section 4.2.2.

4.2.3.2 Impact of Missing Tumor Assessments

The impact of missing scheduled tumor assessments on PFS will be assessed by performing a sensitivity analysis based on the interval censoring analysis methods.

For each patient, the left and the right boundaries of the interval will be derived based on the following rules in Table 3 :

Table 3 Interval Censoring Analysis Method

Situation	Left Boundary	Right Boundary
Participants with disease progression prior to death	The date of the last assessment that shows a progression-free* status	The date of the first assessment that shows disease progression
Participants who died without disease progression	The date of the last assessment that shows a progression-free* status	Date of death
Participants who did not die nor had disease progression	The date of the last assessment that shows a progression-free* status	Not applicable (missing)

*For participants who do not have any post-baseline assessments with progression-free status, the left boundary is the date of randomization.

The PFS survival curves will be estimated by using the nonparametric maximum likelihood estimate (Turnbull 1976) for each treatment arm. The median PFS of each treatment arm will be reported and its 95% confidence interval will be constructed on the basis of the Brookmeyer-Crowley method (Brookmeyer and Crowley 1982).

The stratified log-rank test proposed by Sun (Sun 1996) will be used to compare the PFS in the treatment arms. The treatment effect will be estimated by using a stratified proportional hazards regression model (Finkelstein 1986) with a parametric assumption of piecewise exponential distribution for the baseline hazard function (Friedman 1982, Royston and Parmar 2002). Results from an unstratified analysis will also be provided.

4.2.4 Supplementary Analyses

4.2.4.1 Subgroup Analyses for Primary Estimand/Endpoint

The generalizability of PFS results when comparing divarasib to KRAS G12C inhibitors (sotorasib or adagrasib) will be investigated by estimating the treatment effect in subgroups, including, but not limited to, the following:

- Stratification factors: KEAP1 mutation status, history of CNS metastases, intended KRAS G12C inhibitor in the control arm
- Key baseline demographics: age ($<65, \geq 65$ and $<75, \geq 75$), sex, race, ethnicity, geographic region (Europe vs North America vs rest of world)
- Disease characteristics at baseline: Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs 1), disease staging (stage III vs stage IV), line of therapy (2nd vs $3^{rd}/4^{th}$), programmed death-ligand 1 (PD-L1) status (TPS $<1\%$ vs $1-49\%$ vs $\geq 50\%$), Serine/ Threonine Kinase 11 (STK11) mutation status

Summaries of BICR-assessed PFS by these subgroups will be provided in forest plots including unstratified hazard ratios estimated from Cox proportional hazards models and Kaplan-Meier estimates of the median PFS provided separately for each level of the subgroups.

4.2.4.2 Other Supplementary Analyses for Primary Endpoint/Estimand

To evaluate the consistency of assessments, a concordance analysis of PFS determined by BICR and PFS determined by investigator will be performed by treatment arm and overall. Concordance will be analyzed for Progressive Disease (PD) status (presence of PD vs no-PD) together with the concordance between the date that PD (timing of PD) was reported by BICR vs investigator.

4.3 SECONDARY ENDPOINTS/ESTIMANDS ANALYSES

4.3.1 Key/Confirmatory Secondary Estimands

The attributes describing the key secondary estimands are summarized in Section 1.1. The key secondary endpoints are OS, confirmed ORR, as determined by BICR, and TTCD on the EORTC QLQ-C30 dyspnea item and the physical functioning scale, and the cough scale of the QLQ-LC13.

The formal testing for confirmed ORR and TTCD will be performed once statistical significance is reached for OS (at the time of interim or final OS analysis), based on the data from the primary PFS snapshot.

4.3.1.1 Overall Survival

OS is defined as the time from randomization to death from any cause. OS will be analyzed on the FAS.

Data for participants who are not reported as having died as of the clinical data cutoff date will be censored at the date when they were last known to be alive (or at the time of randomization plus 1 day if no survival follow-up is available after the baseline visit).

For both intercurrent events, a treatment policy strategy will be applied, i.e., OS will be assessed irrespective of whether a participant discontinued early from study drug or started non-protocol anticancer therapy.

Estimation methods will be performed as described for the primary estimand (see Section 4.2.2). The primary comparison of interest is the stratified log-rank test (two-sided 5% significance level) for OS. Critical values at the interim and the final analyses are provided in Section 4.7.1.

Supplementary analyses

Subgroup analyses for OS will be performed as described above for the primary endpoint (see Section 4.2.4.1).

To assess the impact of the intercurrent event of starting a non-protocol specified anticancer therapy (NPT) on OS, the primary analysis of OS will be repeated with such intercurrent event handled using a hypothetical strategy if $\geq$ 10% of participants received NPT in either treatment arm. Rank-preserving structural failure time method will be used

to provide an estimate of the OS time for the treatment arms had NPT not been received (Robins and Tsiatis 1991). This method estimates OS measured from the time of NPT by applying an estimate of the benefit of the NPT. The total OS time (sum of time to NPT and the estimated survival time after NPT is started) will then be analyzed using the same methodology as for the primary analysis of OS.

4.3.1.2 Confirmed Objective Response Rate

Confirmed ORR is defined as the proportion of participants with a complete response or partial response on two occasions $\geq$4 weeks apart, as assessed by BICR according to RECIST v1.1. Participants not meeting this criterion (including participants without a post-baseline tumor assessment) will be considered non-responders. BICR-assessed confirmed ORR will be analyzed on the response-evaluable set (BICR) (see Section 3).

For both intercurrent events defined for the confirmed ORR estimand, a composite variable strategy will be applied. Participants who discontinued early from study drug or started non-protocol anticancer therapy prior to achieving confirmed objective response will be considered non-responders.

An estimate of confirmed ORR and its 95% confidence interval will be calculated by using the Clopper-Pearson method for each treatment arm, and confidence intervals for the difference in confirmed ORRs between the two treatment arms will be determined by using the normal approximation to the binomial distribution.

For formal testing of difference in confirmed ORR between the treatment arms, a covariate-adjusted analysis for the difference of proportions will be conducted using G-Computation (FDA 2023), adjusting for the stratification factors specified in randomization (see Section 1.2.1). The estimate of the covariate-adjusted difference in proportions, together with the estimated standard error and the 95% confidence interval based on bootstrap resampling (FDA 2023) will be presented. Statistical significance will be inferred if the 95% confidence interval for difference in confirmed ORR excludes zero.

Sensitivity analysis

Investigator-assessed confirmed ORR will be analyzed as a sensitivity analysis based on the response-evaluable set (INV).

4.3.1.3 Time to Confirmed Deterioration in Functioning and Disease-related Symptoms

TTCD will be analyzed for the EORTC QLQ-C30 physical functioning scale as well as the EORTC QLQ-C30 dyspnea item and the QLQ-LC13 cough scale.

TTCD is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration that must be held for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death attributable to cancer progression (not death from other causes,

including adverse events [AEs]) within six weeks from the last PRO assessment. A decrease from baseline in the functioning scale of at least 10 points or an increase in the symptom scales of at least 10 points is considered to be clinically meaningful by patients (Osoba et al. 1998).

Regarding intercurrent events, TTCD will be assessed irrespective of whether a participant discontinued early from study drug (i.e., treatment policy strategy), and as if no non-protocol anticancer therapy is started prior to a confirmed clinically meaningful deterioration (i.e., hypothetical strategy). In case of early discontinuation, data collected during follow-up will be included in the analysis. Participants who start NPT without prior clinically meaningful deterioration will be censored at the time of the last assessment before starting the non-protocol specified anticancer therapy. A while-alive strategy will be applied for participants who die before reporting any clinically meaningful deterioration. In case of death without prior deterioration, data will be censored at the last assessment available.

For the analysis of TTCD, participants without confirmed clinically meaningful deterioration as of the clinical data cutoff date (including participants who die without reported clinically meaningful deterioration) will be censored at the time of the last assessment (or at the time of randomization plus 1 day if no assessment was performed after the baseline visit).

Estimation methods will be performed as described for the primary estimand (see Section 4.2.2). The primary comparison of interest for TTCD is the stratified log-rank test (two-sided 5% significance level).

Supplementary analysis

In addition, the change from baseline for the EORTC QLQ-C30 physical functioning scale, EORTC QLQ-C30 dyspnea item and the QLQ-LC13 cough scale will be analyzed using a mixed model for repeated measures (MMRM) with fixed terms for treatment, visit, treatment-by-visit interaction, covariates and the baseline value of the scale. An unstructured covariance matrix will be used. The covariates will be the stratification factors used for randomization.

The statistical model will be used to calculate the difference in adjusted means between the treatment arms at timepoint 3, 6 and 12 months. The adjusted mean (standard error) and 95% confidence interval will be presented for each treatment arm. The difference in adjusted means (standard error) and 95% confidence interval will be presented for each endpoint.

4.3.2 Supportive Secondary Endpoints

4.3.2.1 Duration of Response

Duration of Response (DOR) is defined as the time from the first occurrence of a documented confirmed objective response until the first date that progressive disease or death is documented, whichever occurs first. Disease progression will be determined by BICR according to RECIST v1.1. DOR will be assessed in participants who had an confirmed objective response during the study as determined by BICR. Participants who have not progressed and who have not died as of the clinical data cutoff date for analysis will be censored at the time of the last tumor assessment (or at the date of first confirmed objective response plus 1 day if no tumor assessment was performed after the confirmed objective response).

The DOR analysis will be performed on the basis of a non-randomized subset of participants (specifically, participants who achieve a confirmed objective response); therefore, formal hypothesis testing will not be performed for this endpoint. DOR will be estimated using Kaplan-Meier methodology as described above (see Section 4.2.2). Comparisons between treatment arms will be made for descriptive purposes only.

4.3.2.2 Patient Reported Outcomes

For endpoints collected using EORTC QLQ-C30 and QLQ-LC13 mean scores and changes from baseline will be analyzed descriptively for each timepoint, with baseline defined as the last assessment prior to start of study treatment.

TTCD analyses on the EORTC QLQ-C30 role functioning and global health status (GHS)/ quality of life (QoL) scales and the chest pain scale of the QLQ-LC13 will be performed as described for TTCD key secondary endpoints in Section 4.3.1.3.

Completion rates will be summarized by the number and proportion of participants among those expected to complete the EORTC QLQ-C30 and QLQ-LC13 at each time point for each treatment arm. A questionnaire is considered completed if all questions have been answered.

4.4 EXPLORATORY ANALYSIS

4.4.1 Analyses of Central Nervous System Activity

Analyses of CNS activity will be performed on the FAS.

The probability of CNS progression, non-CNS progression, and death will each be estimated using cumulative incidence functions. CNS progression will be defined as progression due to newly developed CNS lesions and/or progression of previously treated CNS lesions, as determined by BICR according to RECIST v1.1. Estimates of the CNS progression rates at 6, 12 and 18 months with 95% confidence intervals determined on the basis of cumulative incidence functions will be presented.

Time to CNS progression as determined by BICR according to RECIST v1.1, is defined as the time from randomization until first radiographic evidence of CNS progression. To account for the competing risks inherent in such an analysis, stratified and unstratified hazard ratios estimated by Cox regression model will be computed on the basis of cause-specific hazard functions to compare the risk of CNS progression between the treatment arm and the control arm.

Intracranial PFS as determined by BICR according to RECIST v1.1 will be defined as the time from randomization until first radiographic evidence of CNS progression or death from any cause (whichever occurs first). Data for participants without the occurrence of CNS progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment. Intracranial PFS will be estimated using Kaplan-Meier methodology as described above (see Section 4.2.2).

4.4.2 Biomarker Analyses

Exploratory biomarker analyses will be performed in an effort to understand the association of biomarkers with study drug response, including but not limited to efficacy and/or AEs, as well as emergence of resistance. Additional pharmacodynamics analyses will be conducted as appropriate. Exploratory biomarker analyses will include assessments of biomarkers in both tumor tissue and blood. Such assessments will include but will not be limited to mutational analysis (of co-occurring mutations such as *KEAP1*) using NGS and gene expression and may also include other methods that may become available in the future.

4.4.3 Health Status Utility Analyses

EQ-5D-5L Visual Analog Scale (VAS) scores and their change from baseline will be summarized by treatment arm and visit.

Additional health utility data from the EuroQol EQ-5D-5L will be evaluated in pharmacoeconomic models and the results from health economic data analyses will be reported separately from the Clinical Study Report.

4.5 SAFETY ANALYSES

Safety will be assessed through summaries of exposure to study treatment, AEs, changes in laboratory test results, and changes in vital signs and electrocardiograms (ECGs). Safety analyses will be performed on the safety analysis set, unless otherwise stated, according to the treatment that patients actually received. For the control arm safety data will be summarized for individual study drugs (sotorasib and adagrasib separately) as well as for the pooled control arm (sotorasib/adagrasib), if needed.

4.5.1 Extent of Exposure

Study treatment exposure, including treatment duration, number of doses, cumulative dose, and dose intensity, will be summarized by treatment arm with descriptive statistics.

For participants on the control arm exposure data will be summarized by the actual drug received.

4.5.2 Adverse Events

AEs that occur on or after the first dose of study treatment will be considered as treatment-emergent AEs. Only treatment-emergent AEs will be included in safety analyses.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (AEs) (NCI CTCAE) v5.0.

Summary tables by mapped term and appropriate thesaurus level will be provided for the following treatment-emergent events:

- All AEs
- AEs considered to be related to study drug by the investigator
- Common AEs
- AEs with NCI CTCAE grade 3 and 4
- AEs with fatal outcome (Grade 5)
- Serious AEs (SAEs)
- SAEs considered to be related to study drug by the investigator
- AEs leading to drug interruption
- AEs leading to dose reduction
- AEs leading to study treatment discontinuation
- Adverse events of special interest (AESI)

In addition, summary tables by mapped term, appropriate thesaurus level and severity grade:

- All AEs
- AESIs

For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

AESIs for the study treatment will be identified by a set of comprehensive definitions using standardized MedDRA queries (SMQs), High-Level Terms (HLTs) and Sponsor-defined adverse event grouped terms (AEGTs) from the AE clinical database by medical concept. AESIs will be summarized by medical concept, mapped term and severity grade.

Listings of AEs will include all treatment-emergent AEs up to the data cutoff date.

Deaths during the study treatment period and those reported during the follow-up period and causes of death will be summarized by treatment arm.

4.5.3 Additional Safety Assessments

4.5.3.1 Laboratory Data

Relevant laboratory data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade (NCI CTCAE v5.0).

Potential Hy's law patients will be listed. Potential Hy's law cases are defined as elevated alainine trasferase (ALT) or aspartate trasferase (AST) ($>3\times$ upper limit of normal [ULN]) with concomitant elevated total bilirubin ($>2\times$ ULN).

4.5.3.2 Vital Signs

Vital sign data, including pulse rate, respiratory rate, blood pressure, oxygen saturation, and temperature, will be displayed by time, with grades identified where appropriate. Changes in vital signs will be summarized by treatment arm.

4.5.3.3 ECGs

ECG data will be displayed by time, with grades identified where appropriate. Changes in ECGs will be summarized by treatment arm.

4.5.3.4 Clinical Outcome Assessment Safety Analyses

PRO data is collected using the following instruments: Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) and EORTC Item List 46 (IL46). Analyses for PRO-CTCAE and IL46 will be performed for the safety analysis set according to the treatment participants actually received.

PRO-CTCAE

A subset of 12 symptoms deemed most applicable to the current study treatments has been selected for this study.

PRO-CTCAE analyses will be primarily descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities during the study. PRO-CTCAE data will be analyzed at the item level.

PRO-CTCAE data will be summarized over time. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data. The number and percentage of participants reporting each symptom and change from baseline by category (frequency of occurrence, severity, and interference) will be summarized at each assessment timepoint by treatment arm. Additionally, a table will be produced that summarizes the number/proportion of patients reporting symptoms at

baseline, those experiencing a worsening over the course of treatment, and those who deteriorate to a score of 3 or 4. For items that are rated on a 5-point Likert scale, the maximum post-baseline score and change from baseline will be summarized by treatment arm.

Graphical representation of PRO-CTCAE data over time will also be provided.

EORTC IL46

The IL46 is a single question that assesses bother (burden) of treatment. It is rated on a 1 to 4 scale, ranging from "not at all" to "very much."

The analyses of the EORTC IL46 item will be descriptive, with a focus on characterizing the pattern of being troubled by side effects from treatment over the course of the study. The number and percentage of participants reporting each response option ("Not at all" to "Very much") to the item and the change from baseline by response option will be summarized at each assessment timepoint by treatment arm. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Summaries of conduct of study will be provided for the FAS.

Enrollment, study drug administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study drug discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

4.6.2 Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, race/ethnicity, baseline disease characteristics, ECOG Performance Status, and number of prior cancer treatments) as well as stratification factors (KEAP1 mutation status, history of CNS metastasis, intended KRAS G12C inhibitor in the control arm) will be summarized by treatment arm.

A summary of concordance of stratification factors determined by eCRF versus IxRS will also be reported.

4.6.3 Pharmacokinetic Analyses

Pharmacokinetics (PK) analyses will be performed based on the PK-evaluable analysis set (see Section 3) according to the treatment participants actually received.

Individual plasma concentrations of divarasib will be listed and summarized. Divarasib PK data may be pooled and analyzed using the population PK analysis approach, as appropriate, and reported separately from the study report.

Individual plasma concentrations of sotorasib and adagrasib may be listed and summarized. Additional PK analyses (e.g., ex vivo unbound plasma concentration analysis for divarasib, sotorasib, adagrasib) may be conducted as appropriate.

4.7 INTERIM ANALYSES

4.7.1 Planned Interim Analysis

One interim analysis on OS will be performed at the time of the primary PFS analysis. The Lan-DeMets alpha spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994).

The expected number of OS events at the time of the interim analysis is approximately 153 (i.e., 66% information fraction), leading to a stopping boundary in terms of p-value=0.0116 at the interim analysis. Under these assumptions, the critical value for the final OS analysis will be a p-value of 0.0464.

Critical values at the interim and the final analyses will be adjusted according to the actual number of observed OS events per stage to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

5. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

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