Protocol Title:	**A Phase 2, Open-Label, Multicenter Study of the Combination of RMC-4630 and Sotorasib for Non-Small Cell Lung Cancer Subjects with *KRAS*^{G12C} Mutation After Failure of Prior Standard Therapies**
Protocol Number:	RMC-4630-03
EudraCT Number:	2021-003254-23
Compound Number:	RMC-4630
Study Phase:	Phase 2
Short Title:	**Combination Study of RMC-4630 and Sotorasib for Non-Small Cell Lung Cancer Subjects with *KRAS*^{G12C} Mutation After Failure of Prior Standard Therapies**
Sponsor Name:	Revolution Medicines, Inc.
Legal Registered Address:	700 Saginaw Drive Redwood City, CA 94063
Regulatory Agency Identifying Number(s):	IND 138359
Version/Date:	V5.0 / 06 September 2023

SPONSOR SIGNATORY

DocuSigned by:
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Date

Chief Medical Officer, Clinical and Medical Affairs

Sponsor Medical Monitor Name and Contact Information:

[redacted]

Revolution Medicines, Inc.

[redacted]

PROTOCOL SIGNATORY, PRINCIPAL INVESTIGATOR

Title:	**A Phase 2, Open-Label, Multicenter Study of the Combination of RMC-4630 and Sotorasib for Non-Small Cell Lung Cancer Subjects with *KRAS*^{G12C} Mutation After Failure of Prior Standard Therapies**
Protocol No.:	RMC-4630-03
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Compound ID:	RMC-4630
Phase:	2
Sponsor:	Revolution Medicines, Inc.
Regulatory Agency Identifying No.:	IND 138359

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

Principal Investigator's Name (Print)	**Principal Investigator's Signature**
Site Number	**Date (DD/Month/YYYY)**

SUMMARY OF CHANGES

Summary of Changes Since Version 4.0		
Version 5.0	**Amendment Date 06 September 2023**	**Global**
Protocol Amendment Summary and Rationale: This table describes the changes incorporated in Version 5.0 of the protocol. The primary reasons for this amendment are to: • Add an Extended-Use phase to the protocol for subjects experiencing continued clinical benefit from study treatment • Align all countries with a single amendment In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.		

Sections Affected	**Changes**	**Rationale**
Section 1.1.3	Added a brief description of the Extended-Use phase to the Overall Design.	To include the rationale for the Extended-Use phase of the protocol and clarify that LTFU subjects will not be followed in the Extended-Use phase.
Section 1.1.4, Section 4.1.1	Added the Extended-Use phase to the duration of treatment.	To clarify that treatment may continue after the EOS for subjects benefitting from study treatment.
Section 1.1.4, Section 4.1.3	Added duration of Extended-Use phase.	To provide the length of the Extended-Use phase.
Section 1.2 (Figure 1)	Added a footnote to Figure 1 that schema refers to main protocol only.	Clarification of assessment differences between main protocol and Extended-Use phase.
Section 1.3 (Table 1)	• Added text to distinguish assessments for the main protocol from assessments for the Extended-Use phase. • Added columns to the SoA for assessments during the Extended-Use phase and added footnotes for assessments to be performed as clinically indicated and according to local standards of care. • Added a footnote to LTFU.	• To clarify assessments not being performed during the Extended-Use phase. • To describe the assessments to be performed during the Extended-Use phase. • To clarify that LTFU subjects will not be followed in the Extended-Use phase.
Section 1.3 (Table 2)	Added a row for the Extended-Use phase.	To clarify that PK and biomarker sampling will not be performed during the Extended-Use phase.
Section 2.2.2.3	Added hepatotoxicity and QT prolongation if co-administered with drugs known to prolong QT to potential risks.	Update to potential risks.
Section 2.2.2.4	Added prohibition of medications known to prolong QT.	Update to steps to minimize risk.
Section 2.2.2.5	Section was deleted.	COVID-19 pandemic assessments no longer being performed.

Summary of Changes Since Version 4.0			
Version 5.0		**Amendment Date 06 September 2023**	**Global**
Section 4.1.2, Section 7.1, Section 7.2	Removed LTFU from the Extended-Use phase of the study.		To clarify that LTFU subjects will not be followed in the Extended-Use phase.
Section 4.1.4, Section 8.2	Added eligibility for the Extended-use phase and a reference to SoA for Extended-Use phase assessments.		To clarify assessments during the Extended-Use phase.
Section 4.4	Added the LSLV date (EOS) and the Extended-Use phase.		To clarify EOS and Extended-Use phase.
Section 6.1	Added Extended-Use phase to study treatment description.		To describe study treatment administration during the Extended-Use phase.
Section 8.1 Table 1, [footnote 25, footnote 27]	Added text that tumor imaging in the Extended-Use phase is not required per protocol and that subjects in the Extended-Use phase will be managed according to local standards of care.		To clarify assessments and subject management during the Extended-Use phase.
Section 8.2.2	Added to record vital signs in the medical record during the Extended-Use phase.		Clarification for recording of assessments.
Table 1, [footnote 15], Section 8.3.1, Section 8.3.3, Section 8.3.4	Added AE/SAE reporting during the Extended-Use phase.		To clarify AE/SAE reporting changes during the Extended-Use phase.
Section 8.3.5	Added that pregnancy reporting will continue during the Extended-Use phase using the SAE report form.		Clarification of pregnancy reporting.
Section 8.5, Section 8.6	Added that there will not be PK sample collection for treatment of overdose.		To clarify assessment differences between main protocol and Extended-Use phase.
Section 8.8	Added clarification regarding biomarker sample collection.		To clarify assessment differences between main protocol and Extended-Use phase.
Appendix 5	Added text that use and analysis of tumor DNA refers to the main protocol only.		To clarify assessment differences between main protocol and Extended-Use phase.

Abbreviations: AE = adverse event; CRFs = case report forms; EOS = end of study; LTFU = long term follow up; LSLV = last subject last visit; SoA = Schedule of Activities; SAE = serious adverse event.

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1. PROTOCOL SUMMARY

1.1. Synopsis for Protocol RMC-4630-03

Protocol Title: A Phase 2, Open-Label, Multicenter Study of the Combination of RMC-4630 and Sotorasib for Non-Small Cell Lung Cancer (NSCLC) Subjects with *KRAS*^{G12C} Mutation After Failure of Prior Standard Therapies

Short Title: Combination Study of RMC-4630 and Sotorasib for NSCLC Subjects with *KRAS*^{G12C} Mutation After Failure of Prior Standard Therapies

1.1.1. Rationale

The RAS signaling pathway is frequently dysregulated in human cancers, typically as a result of genomic alterations that lead to hyperactivation (Dhillon, 2007). These alterations can occur at 3 levels: upstream of RAS in receptor tyrosine kinases (RTKs), directly within mediators of the RAS catalytic cycle (RAS isoforms and RAS-GTPase activating proteins [GAPs], such as *neurofibromin 1* [*NF1*]), or in downstream effector kinases, such as *BRAF* or MEK (TCGA Network, 2014).

Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP2) is a positive upstream regulator of RAS activation. Thus, SHPs presents a suitable therapeutic target for patients whose tumors harbor oncogenic mutations that remain dependent on active RAS cycling between guanosine triphosphate (GTP)- and guanosine diphosphate (GDP)-bound states. Examples of these include subsets of *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*)^{G12}, mutations in *NF1* predicted to result in loss of function (*NF1*^{LOF}) mutations, Class 3 type mutations in *BRAF* (Nichols, 2017; Nichols 2018), or amplification of wild-type *KRAS* (Wong, 2018). Preclinical studies demonstrated that daily oral (PO) administration of a SHP2 inhibitor alone (at the maximum tolerated dose [MTD]) achieved tumor cytostasis in cell-line-derived xenograft (CDX) and patient-derived xenograft (PDX) models harboring these mutations, and in some instances, tumor regressions (Nichols, 2017; Nichols, 2018; Wong, 2018).

The *KRAS* p.G12C mutation has been identified as an oncogenic driver in several types of solid tumors including NSCLC, colorectal cancer (CRC), and other solid tumors. However, effective targeted therapies for *KRAS*-mutant cancers remain an unmet clinical need. Two inhibitors, sotorasib and adagrasib, are currently in clinical trials in subjects with advanced *KRAS*^{G12C} mutated solid tumors (NCT03600883 [sotorasib] and NCT03785249, NCT04685135, NCT04330664, and NCT04613596 [adagrasib]). Data reported from these early clinical trials have shown favorable safety profiles and some promising monotherapy responses in patients with NSCLC (Canon, 2019; Hallin, 2020; Hong, 2020, Jänne, 2020; Johnson, 2020; Li, 2021).

On 28 May 2021, the United States (US) Food and Drug Administration (FDA) granted accelerated approval to sotorasib (LUMAKRAS™) for adult patients with *KRAS*^{G12C}-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy. The European Medicines Agency (EMA) recently granted conditional approval on 12 November 2021 of LUMYKRAS® (sotorasib) in patients with *KRAS*^{G12C}-mutated advanced NSCLC. Based on Amgen's public release announcement on 09 January 2022, the European Commission (EC) has granted conditional marketing authorization for LUMYKRAS® (sotorasib). The approval was based on CodeBreaK 100, a multicenter, single-arm, open label clinical trial (NCT03600883) that included subjects with locally advanced or metastatic NSCLC with *KRAS*^{G12C} mutations.

Efficacy was evaluated in 124 subjects whose disease had progressed on or after at least one prior systemic therapy. Subjects received sotorasib [redacted] PO once daily (QD) until disease progression or unacceptable toxicity. The main efficacy outcome measures were objective response rate (ORR), according to Response Evaluation Criteria in Solid Tumours, Version 1.1 (RECIST v1.1), as evaluated by blinded independent central review and response duration. The ORR was 36% (95% confidence interval [CI]: 28%, 45%) with a median response duration of 10 months (range 1.3+, 11.1). The most common adverse reactions (≥ 20% of subjects) were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. The most common laboratory abnormalities (≥ 25% of subjects) were decreased lymphocytes, decreased hemoglobin, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased calcium, increased alkaline phosphatase (ALP), increased urine protein, and decreased sodium. The recommended sotorasib dose is [redacted] PO QD with or without food. The Sponsor notes that data readout from a post-marketing study of sotorasib dose optimization in patients with advanced NSCLC who have received one prior therapy (see NCT03600883 found on ClinicalTrials.gov) is imminent at the time of this protocol amendment. If supported by the data, at the Sponsor's discretion, new subjects enrolling on this trial may be treated at the lower sotorasib dose of [redacted] in combination with RMC-4630 (see Table 4 and Table 5). Subjects currently enrolled at [redacted] in combination with RMC-4630 may continue at their current dose or dose reduce based on discussion with the Sponsor Medical Monitor. Subjects developing toxicities at sotorasib [redacted] may dose reduce to sotorasib [redacted] or discontinue treatment.

Despite encouraging early clinical data in monotherapy, not all second- or third-line treatments for NSCLC patients with *KRAS*^{G12C}-mutated tumors are effective. (Hong, 2020) has reported an objective response rate (ORR) to sotorasib of 32%, and (Jänne, 2020) has reported an ORR to adagrasib of 45%. Therefore, improvements in therapy are needed for patients with *KRAS*^{G12C} NSCLC after failure of prior standard therapies. In addition, biomarkers, such as comutation of *STK11/LKB1* and/or *KEAP1,* appear to delineate subpopulations that are relatively less responsive to standard-of-care NSCLC therapy (Singh, 2021); these comutations also may influence the response rate to sotorasib monotherapy (Li, 2021).

Preclinical data demonstrates that the potency of *KRAS*^{G12C} inhibitor treatment can be modulated by upstream RTK activation (Lito, 2016), which occurs as an adaptive response to inhibition of *KRAS*^{G12C} OFF state with either sotorasib or adagrasib. Concurrent inhibition of RTK signaling can optimize the RAS signaling pathway in *KRAS*^{G12C} tumors (Lito, 2016; Canon, 2019). The addition of a SHP2 inhibitor like RMC-4630 to *KRAS*^{G12C}OFF state inhibitors improves tumor responses in preclinical models (Hallin, 2020; Liu, 2018), and can also abrogate *KRAS* signaling, eliminate residual or bypass upstream RTK activity, and thereby potentially lead to greater combinatorial efficacy and deeper, more durable responses. Phase 1b clinical trials combining *KRAS*^{G12C}OFF-state inhibitors with SHP2 inhibitors are currently ongoing, but the data are not yet available.

RMC-4630 and sotorasib combination therapy is being tested in an ongoing Amgen-sponsored Phase 1b platform Study (CodeBreaK 101 [NCT04185883], Subprotocol C, hereafter referred to as CodeBreaK 101C). CodeBreaK 101C was initiated in May 2020 and is currently dosing subjects at RMC-4630 [redacted] twic[redacted]) on [redacted] [redacted] of each week in a 21-day cycle (ie, Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle). The study has tested and cleared lower dose levels of RMC-4630, which include both [redacted] of each week in a

21-day cycle (ie, Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) and [redacted] on Day 1 and Day 4 (D1D4) of each week in a 21-day cycle (ie, Days 1, 4, 8, 11, 15, and 19 of each 21-day cycle) in combination with of sotorasib QD.

This protocol (RMC-4630-03) is a Phase 2 study designed to complement the ongoing CodeBreaK 101C study and will further characterize the efficacy, safety, pharmacokinetics (PK), and tolerability of RMC-4630 and sotorasib combination therapy for subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC who have received at least one prior systemic therapy.

Emerging clinical data from sotorasib monotherapy and adagrasib monotherapy suggest that *KRAS*^{G12C}-mutated NSCLC could represent a heterogenous population defined by comutations such as STK11 and KEAP1 (Li, 2021; Jänne, 2020). Preclinical data suggest SHP2 resistance in select tumors including those harboring *BRAF Class 1* and *2* and *neuroblastoma RAS viral oncogene homolog* (*NRAS*) mutations (Nichols, 2018). Leveraging these learnings, this study will prospectively define analysis of subpopulations of *KRAS*^{G12C}-mutated NSCLC without or with detectable comutations that might influence the outcome to sotorasib (eg, *STK11*, *KEAP1*) and/or RMC-4630 (eg, *BRAF*, *NRAS*).

1.1.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the antitumor effects of RMC-4630 and sotorasib in locally advanced or metastatic NSCLC subjects with *KRAS*^{G12C} mutation with and without co-existing genetic aberrations in specific genes such as *STK11/LKB1, KEAP1,* and *PIK3CA* (see detailed list in Appendix 9) after failure of prior standard therapy	ORR as assessed per RECIST v1.1
Secondary	
• To characterize the safety, tolerability, and PK of RMC-4630 in combination with sotorasib for subjects with *KRAS*^{G12C} mutant NSCLC after failure of prior standard therapy • To further characterize efficacy of RMC-4630 in combination with sotorasib as assessed by DOR, DCR, PFS, and OS in subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC after failure of prior standard therapy	• Incidence, nature, and severity of TEAEs, SAEs, clinically significant changes in laboratory tests, ECGs, and vital signs • Trough and approximate peak concentrations of RMC-4630 and sotorasib • DOR, DCR, and PFS as assessed per RECIST v1.1, and OS
Exploratory	
• To explore PK relationships with safety and/or efficacy endpoints • To investigate potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor tissue samples	• Sotorasib and RMC-4630 exposure/safety and exposure/efficacy relationships • Quantification of biomarker expression (protein, RNA, and DNA levels) as appropriate in ctDNA and archival tumor tissues (or fresh, if archival tumor is not available).

Abbreviations: ctDNA = circulating tumor deoxyribonucleic acid; DCR = disease control rate; DOR = duration of response; DNA = deoxyribonucleic acid; ECG = electrocardiogram; *KEAP1 = Kelch-like ECH-associated protein 1*; *KRAS*^{G12C} = *KRAS* with a mutation at codon 12, which encodes glycine (G) to cysteine (C); NSCLC = non–small-cell lung cancer; *LKB1 = liver kinase B1*; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; *PIK3CA = phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha*; PK = pharmacokinetic(s); RECIST v1.1 =

Response Evaluation Criteria in Solid Tumours, Version 1.1; RNA = ribonucleic acid; SAE = serious adverse event; *STK11* = *serine/threonine kinase 11*; TEAE = treatment-emergent adverse event.

1.1.3. Overall Design

This is a phase 2 multicenter, open-label study evaluating the efficacy, safety, tolerability, and pharmacokinetics (PK) of RMC-4630 in combination with sotorasib in subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC after failure of prior standard therapy. The overall study schema is illustrated in Figure 1. The study will be conducted at approximately [redacted] clinical sites globally and is expected to enroll up to approximately [redacted] subjects.

Prior to enrollment, all subjects will undergo screening to determine study eligibility. Eligibility will be assessed based on inclusion and exclusion criteria (Sections 5.1 and 5.2, respectively) and prior/local genomic testing reports from a tumor biopsy or plasma sample. Information on the presence of any genotypic aberrations in the tumor will be collected for all subjects based on prior/local genomic testing reports. Mutation testing results for all subjects must have been obtained in a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP) certified laboratory and collected preferably within 3 years of the subject's study enrollment. See Appendix 9 for details of genotypic mutations required for enrollment. Subjects may remain in the study, regardless of the results of central laboratory testing, unless other exclusionary criteria are met, or the subject withdraws consent.

This Phase 2 study will have a safety run-in period where RMC-4630 will be administered at a starting dose of [redacted] on [redacted] of each week in a 21-day cycle (ie, Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) and sotorasib [redacted] QD in a 21-day cycle. Subjects will be evaluated for dose -limiting toxicities (DLTs) (Section 8.4). The decision to escalate the RMC-4630 dose to [redacted] on [redacted] of each week in a 21-day cycle (ie, Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) will be guided by a modified toxicity probability interval 2 (mTPI-2) algorithm (see Appendix 11) and made by the Dose Committee. After completion of the safety run-in (DLT clearance) of both dose levels, additional subjects may be enrolled into one or both dose cohorts for the purpose of dose optimization before selecting the final expansion dose. Expansion may commence as soon as the expansion dose has been selected from either CodeBreaK 101C or this study, whichever occurs first. The Sponsor may proceed directly to dose expansion without completing the safety run-in period. The combination dose for expansion will be determined by the Sponsor after taking into consideration the totality of available data from CodeBreaK 101C and the cumulative data from this study. The Sponsor notes that data readout from a post-marketing study of sotorasib dose optimization in patients with advanced NSCLC who have received one prior therapy (NCT03600883) is imminent at the time of this protocol amendment. If supported by the data, at the Sponsor's discretion, new subjects enrolling on this trial may be treated at a lower sotorasib dose of [redacted] in combination with RMC-4630 (see Table 4 and Table 5). Subjects currently enrolled at sotorasib dose of [redacted] in combination with RMC-4630 may continue at their current dose of sotorasib or dose reduce based on discussion with the Sponsor Medical Monitor. Subjects developing toxicities at sotorasib 240 mg QD may dose reduce to sotorasib [redacted] or discontinue treatment.

The study will enroll a total of approximately [redacted] globally. Subjects will be categorized into 1 of 2 cohorts.

- Cohort 1 will be the primary cohort of this study and will consist of *KRAS*^{G12C} NSCLC subjects **without** potential genetic aberrations in specific genes, such as *STK11/LKB1, KEAP1*, and *PIK3CA* (see detailed list in Appendix 9).
- Cohort 2 will consist of *KRAS*^{G12C} NSCLC subjects **with** co-existing genetic aberrations in specific genes, such as *STK11/LKB1, KEAP1*, and *PIK3CA* (see detailed list in Appendix 9). Additional details of the sample size and statistical considerations are provided in Section 9.

Subjects may remain on study drug until disease progression per RECIST v1.1, unacceptable toxicity, or other criteria for withdrawal are met, whichever occurs first. The End-of-Study (EOS) is defined as the date of the last visit of the last subject in the study (ie, last subject, last visit [LSLV]) or 12 months after the last subject is enrolled, whichever occurs first. Subjects benefitting from administration of RMC-4630 and sotorasib may continue to receive study treatment until disease progression or unacceptable toxicity as part of an Extended-Use phase of the protocol.

Upon permanent discontinuation of study treatment for any reason, including for subjects in the Extended-Use Phase, an end-of-treatment (EOT) visit should be completed within 30 days after the last dose of study treatment or before any new antitumor treatment is started.

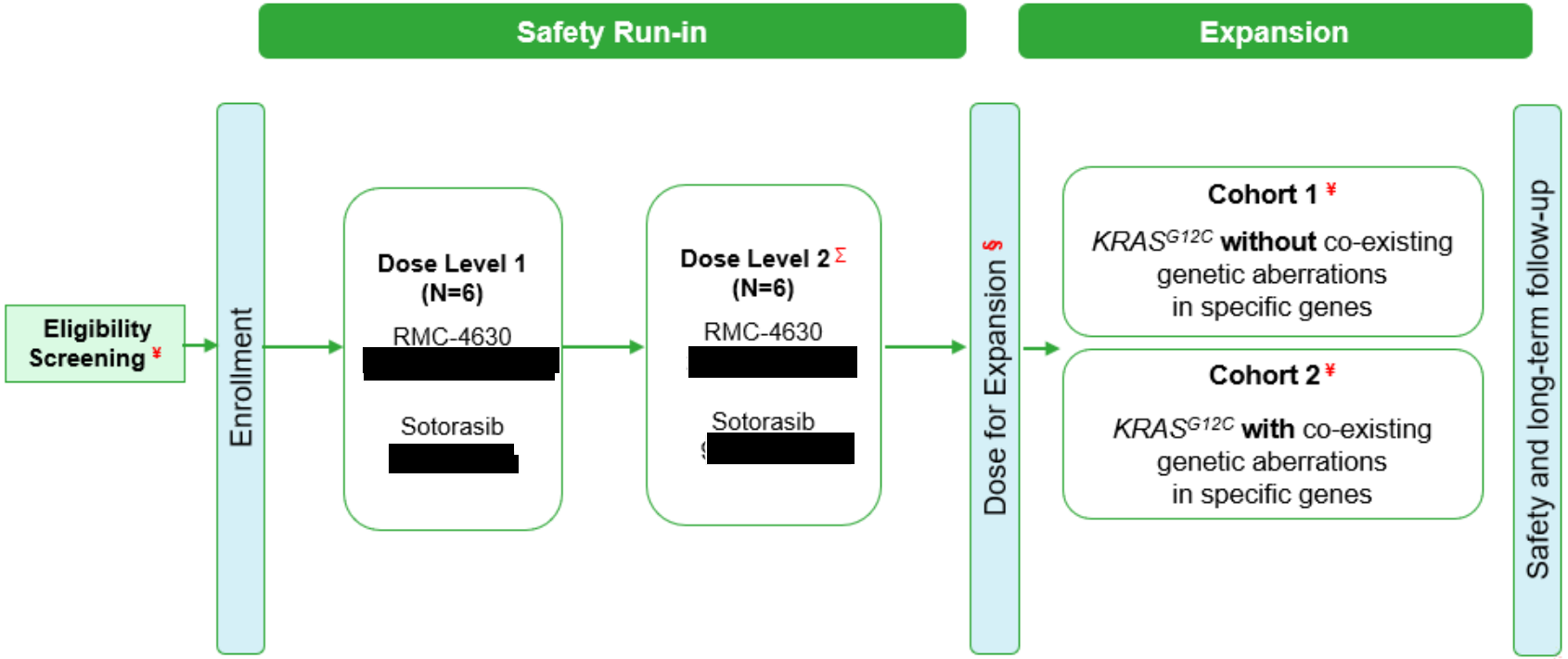
Following the EOT visit, subjects will be considered to have completed the study. Survival follow up will be discontinued for subjects currently in LTFU.

1.1.4. Duration of Therapy

Subjects will be permitted to remain on study treatment until disease progression per RECIST v1.1, unacceptable toxicity, or other criteria for withdrawal are met (see Section 7.1, whichever comes first. Subjects will return to the clinical site for an EOT visit within 30 days after their last dose of study treatment. Subjects who are benefitting from study treatment at the time of the EOS may continue treatment in the Extended-Use phase of the study, which will be conducted through June 2024.

1.2. Schemas

Figure 1: RMC-4630-03 Study Schema



Abbreviations: ctDNA = circulating tumor deoxyribonucleic acid; [redacted] of *each week* in a 21-day cycle (ie, Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle); $KRAS^{G12C}$ = *KRAS* with a mutation at codon 12, which encodes glycine (G) to cysteine (C); mTPI-2 = modified toxicity probability interval-2; QD = once daily.

Note: The study schema refers the main protocol only.

¥ Eligibility for study entry will be based on existing genomic reports from a qualified or validated test. Retrospective ctDNA may identify comutation(s) that may shift subjects from Cohort 1 to Cohort 2.

Σ The starting dose is [redacted] on [redacted] of each week in a 21-day cycle (ie, Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) and escalation to [redacted] of *each week* in a 21-day cycle (ie, Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle) will be guided by an mTPI-2 algorithm (Appendix 11) and made by the Dose Committee.
At the Sponsor's discretion, new subjects enrolling on this trial may be treated at the lower sotorasib dose of [redacted] in combination with RMC-4630 instead of [redacted] in combination with RMC-4630 (see Table 4 and Table 5).

§ Expansion in this study may commence as soon as the expansion dose has been selected from either CodeBreaK 101C or RMC-4630-03, whichever occurs first. The Sponsor may proceed directly to dose expansion without completing the safety run-in period. The combination dose for expansion in this study will be determined by the Sponsor after taking into consideration the totality of available data from both CodeBreaK 101C and cumulative data from this study. After completion of the safety run-in (DLT clearance) of both dose levels, additional subjects may be enrolled into one or both dose levels for the purpose of dose optimization to inform final expansion dose selection.

1.3. Schedule of Activities (SoA)

Weekends and national holidays do not count towards visit windows and will not be considered protocol deviations.

For subjects continuing study treatment beyond Cycle 2, the clinic visits are reduced to D1 of each cycle. If clinically indicated, subjects can be seen at any time in the clinic for an unscheduled visit. The SoA is presented in Table 1.

Note that assessments from Screening through LTFU are for the main protocol only. Assessments performed during the Extended-Use phase will occur as clinically indicated, unless specified otherwise.

Table 1: Schedule of Activities for Protocol RMC-4630-03

Cycle/Day	Screening[1]		Treatment								EOT/ EOS[2]	LTFU[3]	Extended -Use[4]	Extended -Use EOT/ EOS[2]
			Cycle 1 (21-Days)			Cycle 2 (21-Days)		Cycle 3 (21-Days)	D1 of Every Cycle (After C3)	D1 of Every Other Cycle (After C3)				
Day	**-28 to 1**	**-14 to 1**	**1**	**8 (±1D)**	**15 (±1D)**	**1 (±1D)**	**15 (±1D)**	**1 (±1D)**	**1 (±1D)**	**1 (±1D)**	**(+30D)**	**(±14D)**	**After Main EOS**	**(+30D)**
General and Safety Assessments														
Informed[5] Consent	X												X	
Demographics[6]	X													
Medical/Surgical/ Cancer History[7]	X													
Smoking Status	X													
Documentation of *KRAS*^{G12C} Mutation[8]	X													
Complete Physical Examination[9]		X				X					X			
Limited Physical Examination[10]			X	X	X		X	X	X					X
Vital Signs[11]		X	X	X	X	X	X	X	X		X		X	X
Body Weight and Height[12]		X	X			X		X	X		X		X	X
12-Lead ECG[13]		X	X		X			X		X	X		X	X

Table 1: Schedule of Activities for Protocol RMC-4630-03 (Continued)

Cycle/Day	Screening[1]		Treatment								EOT/ EOS[2]	LTFU[33]	Extended -Use[34]	Extended - Use EOT/ EOS[2]
			Cycle 1 (21-Days)			Cycle 2 (21-Days)		Cycle 3 (21-Days)	D1 of Every Cycle (After C3)	D1 of Every Other Cycle (After C3)				
Day	**-28 to 1**	**-14 to 1**	**1**	**8 (±1D)**	**15 (±1D)**	**1 (±1D)**	**15 (±1D)**	**1 (±1D)**	**1 (±1D)**	**1 (±1D)**	**(+30D)**	**(±14D)**	**After Main EOS**	**(+30D)**
ECHO/MUGA[14]	X					X					X			
ECOG PS[15]		X	X		X	X		X	X		X		X	X
Ophthalmologic Examination[16]	X													
Adverse Events[17]		X	X	X	X	X	X	X	X		X		X	X
Concomitant Medications[18]		X	X	X	X	X	X	X	X		X		X	X
Assessment and Documentation of Study Treatment Compliance[19]			X	X	X	X	X	X	X		X		X	X
Hematology Panel[20]		X	X	X	X	X	X	X	X		X		X	X
Serum Chemistry Panel[21]		X	X	X	X	X	X	X	X		X		X	X
Coagulation Tests (PT, INR, and aPTT or PTT)[22]		X	X					X		X	X		X	X
Urinalysis[23]		X	X					X			X		X	X

Table 1: Schedule of Activities for Protocol RMC-4630-03 (Continued)

Cycle/Day	Screening[1]		Treatment								EOT/ EOS[2]	LTFU[33]	Extended -Use [34]	Extended -Use EOT/ EOS[2]
			Cycle 1 (21-Days)			Cycle 2 (21-Days)		Cycle 3 (21-Days)	D1 of Every Cycle (After C3)	D1 of Every Other Cycle (After C3)				
Day	**-28 to 1**	**-14 to 1**	**1**	**8 (±1D)**	**15 (±1D)**	**1 (±1D)**	**15 (±1D)**	**1 (±1D)**	**1 (±1D)**	**1 (±1D)**	**(+30D)**	**(±14D)**	**After Main EOS**	**(+30D)**
Pregnancy Test (FSH and Estradiol, if needed)[24]		X	X			X		X	X		X			X
Hepatitis B and C Virus Tests[25]	X													
CPK (Total and MM Isoenzymes)[26]			X		X	X		X	X		X			
CT Scan[27]	X							X (±1 week)		X (every 2 cycles then every 4 cycles [±1 week] starting at C9)	X			
Brain MRI[28]	X													
RECIST v1.1 Tumor Response Assessment[29]								X (±1 week)		X (every 2 cycles then every 4 cycles [±1 week] starting at C9)	X			X
Study Treatment Administration														
RMC-4630[30]			<[redacted]										X	
Sotorasib[31]			<---------- Dosed QD---------->										X	

Table 1: Schedule of Activities for Protocol RMC-4630-03 (Continued)

Cycle/Day	Screening[1]		Treatment								EOT/ EOS[2]	LTFU[33]	Extended -Use[34]	Extended - Use EOT/ EOS[2]
			Cycle 1 (21-Days)			Cycle 2 (21-Days)		Cycle 3 (21-Days)	D1 of Every Cycle (After C3)	D1 of Every Other Cycle (After C3)				
Day	**-28 to 1**	**-14 to 1**	**1**	**8 (±1D)**	**15 (±1D)**	**1 (±1D)**	**15 (±1D)**	**1 (±1D)**	**1 (±1D)**	**1 (±1D)**	**(+30D)**	**(±14D)**	**After Main EOS**	**(+30D)**
PK and Biomarker Assessment														
PK Sampling[32]			See Table 2											
Blood for ctDNA biomarker[33]			See Table 2								X			
Archival tumor tissue (FFPE) for solid tumors or fresh-tissue biopsy[34]	X													
Long-Term Follow-up														
Telephone contact for survival status[3]			Only completed after EOT									X		

[1] Screening window is 14 days, unless otherwise specified. Informed consent and subject demographics, medical history, smoking status, documentation of tumor genotypic mutations, screening hepatitis tests, CT/MRI scan, ECHO/MUGA, and ophthalmic examination may be obtained 28 days before C1D1.

[2] Subjects who discontinue study treatment should complete the EOT visit within 30 days of last dose of study treatment. Subjects who wish to withdraw from treatment should be encouraged to complete the EOT assessments. If a subject chooses to withdraw from the study completely, record the reason for withdrawal on the appropriate page(s) of the eCRF. Subjects who are on treatment at the main EOS and are deriving clinical benefit from RMC 4630 and sotorasib will be considered for enrollment in a separate Extended-Use phase. These subjects should enter the Extended-Use phase without interruption of treatment and should complete main EOT assessments to receive treatment on Day 1 of the Extended-Use phase. EOT/EOS for the Extended-Use phase will be performed within 30 days of the last dose in the Extended-Use phase.

[3] After termination of treatment, subjects in the main study will remain on study for survival follow-up. Survival follow up will be discontinued for subjects currently in LTFU at the time of the initiation of the Extended-Use phase.

[4] Assessments performed during the Extended-Use phase will occur as clinically indicated, unless specified otherwise.

[5] Obtain written informed consent from the subjects before any protocol required procedures and assessments are performed. Standard of care evaluations performed as part of the subject's routine treatment prior to signing consent may be used if they were done in the timeframe required for screening.

[6] Demographic information includes the following: age, gender, race, and ethnicity.

[7] Prior cancer history includes: (i) date of diagnosis, (ii) staging, (iii) all previous therapies (ie, chemotherapy, immunotherapy, biologic or targeted agents, experimental therapies, radiotherapy, and surgery), (iv) previous therapy details (ie, regimen, start and stop dates), (v) best response for each regimen, (vi) date of relapse or disease progression, and (vii) any molecular characterization of tumor (eg, PD-L1 expression).

[8] Documentation of KRASG12 NSCLC in a prior genomic report within 3 years of study enrollment. Please see Appendix 9 for a detailed list of genetic aberrations, which may be allowed for subjects enrolling in Cohort 2 of the dose expansion portion of the study.

[9] Complete physical examination should be performed during screening, C2D1, and at EOT. The examination should include an evaluation of the HEENT, dermatologic, cardiovascular, respiratory, GI (including assessments of liver and spleen), musculoskeletal, neurological, and lymphatic systems. A symptom/AE-directed physical examination should be performed as indicated by subject presentation or reported symptoms or AEs. New or worsened abnormalities should be recorded as AEs, if appropriate.

[10] Limited physical examination should be performed on C1D1, C1D8, C1D15, C2D15 and C3D1 and D1 of each subsequent cycle and should include evaluation of HEENT, dermatologic, cardiovascular, respiratory, and GI systems. A symptom/AE-directed physical examination should be performed as indicated by subject presentation or reported symptoms or AEs. New or worsened abnormalities should be recorded as AEs, if appropriate.

[11] Vital signs include the following: temperature, blood pressure preferably in seated position, pulse rate, pulse oximetry, and respiratory rate. Vital signs should be taken prior to administration of study treatment.

[12] Height and Weight should be measured during screening for the purposes of documentation. Only weight is measured at the remaining timepoints, and weight may be measured and recorded at other time points if clinically indicated at the investigator's discretion. Abnormalities including >10% weight change, should be recorded as AEs, if appropriate.

[13] ECGs should be performed on all subjects in the supine position. A single ECG may be performed at Screening, but the average of triplicate readings for assessing QTc interval may be used at Screening to determine eligibility. Triplicate ECGs should be performed at C1D1 and C1D15 pre-dose and again approximately 2-4 hours post-dose. Then a single pre dose ECG should be obtained on D1 of every 2 cycles starting at C3 (eg, C3D1, C5D1, etc) and at EOT. During the Extended-Use phase, ECGs will be performed according to local standards of care.

[14] ECHO is the preferred methodology to measure LVEF. MUGA may be used if ECHO is not available or not technically feasible. However, the same methodology should be used throughout the study. Assessments should be performed during screening, on C2D1 (+7 days), EOT, and if clinically indicated at any point. If a subject does not complete 2 cycles of study treatment, the EOT assessment of LVEF is not required unless clinical signs or symptoms warrant an examination. All subjects who require dose reduction of study treatment due to decrease in LVEF should have ECHO at the end of each cycle for 2 more cycles and then if clinically indicated to ensure that subject is not experiencing a decrease in LVEF even with a reduced dose.

[15] ECOG PS to be assessed at screening, C1D1, C1D15, and D1 of each subsequent cycle beginning at C2, and at EOT. During the Extended-Use phase, ECOG PS will be assessed according to local standards of care.

[16] Ophthalmic examination if clinically indicated, including full fundoscopic examination and optical coherence tomography should be performed by an ophthalmologist. Additional examinations should be performed as clinically indicated.

[17] Monitor and record AEs and SAEs throughout the main study. Record all AEs, regardless of relationship to study treatment, that occur after initiation of first study treatment until EOT. All AEs and SAEs will be collected from the start of treatment until 30 days after the last dose, or upon initiation of alternative cancer treatment, whichever occurs first. After this period, investigators should report only SAEs that are thought to be related to RMC 4630 and/or sotorasib. After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol mandated intervention will be collected (eg, SAEs related to invasive procedures such as biopsies or medication washout). All SAEs that occur should be reported to the Sponsor or designee within 24 hours of investigator awareness. All AEs (regardless of relationship to study treatment) and SAEs determined not to be study- treatment related (ie, not related and unlikely related)

will be followed through the last study visit and be noted as "continuing" if not resolved at this visit. Any SAE that is determined to be study treatment related (possibly, probably, or definitely related) will be followed to resolution or stabilization, until it is determined to be irreversible by the investigator, the subject is lost to follow up, or it has been determined that the study treatment is not the cause of the AE/SAE. AE/SAE reporting will end after the subject initiates alternative cancer treatment. During the Extended-Use phase of the study, only SAEs (irrespective of causality) and related AEs will be reported in the EDC. All SAEs will also be reported on the SAE Report Form.

[18] Record all concomitant medications including any prescription medications, over the counter preparations, and transfusions received by subject from 7 days preceding C1D1 through EOT. During the Extended-Use phase, concomitant medications given for SAEs only will be recorded.

[19] Subjects should be instructed to bring their pills and diary to every clinic visit, or to submit diary information at that time.

[20] Hematology includes the following: RBC count, hemoglobin, hematocrit, MCV, MCH, % reticulocytes, platelet count, WBC count, and differential (neutrophils, bands [if available], lymphocytes, monocytes, eosinophils, basophils, other cells). NOTE: Testing must be performed and reviewed before dosing on C1D1. If hematology samples are obtained within the previous 72 hours as part of screening, then re-testing on C1D1 is not required. For subsequent visits after C1D1, samples may be obtained up to 72 hours prior to the visit. During the Extended-Use phase, hematology testing will be performed according to local standards of care.

[21] Serum chemistry includes the following: sodium, potassium, chloride, bicarbonate/carbon dioxide, BUN, creatinine, glucose (non-fasting), albumin, total protein, calcium, magnesium, phosphorus, uric acid, lipase, GGT, ALT, AST, total and direct bilirubin, and ALP. NOTE: Perform tests and review results before dosing on C1D1. If chemistry samples were obtained within the previous 72 hours as part of screening, then re-testing on C1D1 is not required. Plasma is permitted. For subsequent visits after C1D1, samples may be obtained up to 72 hours prior to the visit. During the Extended-Use phase, serum chemistry testing will be performed according to local standards of care.

[22] Coagulation studies to include PT, INR and aPTT/PTT during screening, C1D1, C3D1, every other subsequent cycle after C3D1, and EOT. Additional testing may be performed if clinically indicated. If coagulation samples were obtained within the previous 72 hours as part of screening, then re-testing on C1D1 is not required. For subsequent visits after C1D1, samples may be obtained up to 72 hours prior to the visit." During the Extended-Use phase, coagulation testing will be performed according to local standards of care.

[23] Urinalysis includes the following: appearance, pH, specific gravity, glucose, protein/albumin, blood, ketones, bilirubin, nitrites, urobilinogen, and leukocyte esterase. In addition, a microscopic examination for casts, crystals, and cells may be performed if feasible and clinically indicated. If urinalysis samples were obtained within the previous 72 hours as part of screening, then re-testing on C1D1 is not required. For subsequent visits after C1D1, samples may be obtained up to 72 hours prior to the visit. During the Extended-Use phase, urinalysis will be performed according to local standards of care.

[24] For females of childbearing potential (including tubal ligation), perform a blood pregnancy test at screening and a urine/blood pregnancy test pre-dose within 72-hours of D1 of each cycle, as well as at the EOT. A positive urine pregnancy test must be confirmed with a blood test. For all other women, documentation of non-childbearing potential must be present in the medical history. Perform FSH and estradiol tests as needed, in women of non-childbearing potential only.

[25] Hepatitis serology includes HBsAg, HBcAb, and HCV antibody. Additional testing (eg, hepatitis B viral load, HBsAb, hepatitis B core IgM antibody) may be required if results are inconclusive or positive for surface antigen/core antibody.

[26]CPK levels should be obtained within 72-hours of C1D1, C1D15, and D1 of each cycle, EOT and if clinically indicated.

[27]Tumor imaging should be performed at screening and every 2 cycles starting from Cycle 3 (ie, every 6 weeks [±1 week]) up to Cycle 9, every 4 cycles (ie, every 12 weeks [±1 week]) thereafter and EOT. Tumor assessments should include CT scans (with contrast) or MRI of the chest and abdomen (depending on primary tumor type, site of metastasis, and investigator assessment). At the investigator's discretion, the imaging studies may be repeated at any time if disease progression is suspected. Additional studies, such as PET scans or bone scans to confirm presence of new lesions, should be performed if clinically indicated. Every effort should be taken to repeat the same modality used at screening throughout the study and to ensure all anatomy imaged at screening is again imaged at follow up scans for any given subject. Please note that the window for CT/MRI and tumor assessments is ± 7 days. Radiographic response (CR and PR) requires confirmation by a repeat scan at least 4 weeks after the first documentation of response and may be delayed until the next scheduled scan to avoid

unnecessary procedures. An EOT scan is not needed if it was already performed at the time of disease progression and the subject discontinued study treatment due to disease progression. In the Extended-Use phase, tumor imaging is not required per protocol. If required, imaging should be performed according to local standards of care.

[28]Required within 4 weeks of C1D1 for subjects with previous history of brain metastases or suspected brain metastasis to establish stable disease.

[29]Measurable disease is required for each subject. All measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response assessments will be assessed by the investigator, based on physical examinations and CT scans or MRI using RECIST v1.1 (Appendix 6). As part of tumor assessment, physical examinations should include all areas of tumor involvement that are amenable to examination including biopsy sites, lymph nodes, and bone tenderness, if applicable. Scans should be performed every 2 cycles until Cycle 9, and every 4 cycles thereafter. During the Extended-Use phase, tumor imaging is not required per protocol. Response assessments will be performed according to local standards of care and may be reported in the eCRF at the end of the extended use phase, if available.

[30]RMC 4630 BIW dosing should be administered PO on D1 and D2. During clinic visit days in C1, as well as D1 of subsequent cycles, RMC 4630 should be administered in the clinic in order to comply with blood PK, ctDNA, or ECG assessment timepoints.

[31]Initially, subjects will be dosed sotorasib 960 mg QD PO. If supported by the data from a post-marketing study of sotorasib dose optimization in patients with advanced NSCLC who have received 1 prior therapy, at the Sponsor's discretion, new subjects enrolling on this trial may be treated at sotorasib 240 mg QD in combination with RMC-4630. Subjects currently enrolled at 960 mg may continue at their current dose or dose reduce based on discussion with the Sponsor's Medical Monitor. Subjects developing toxicities at sotorasib 240 mg QD in combination with RMC-4630 may dose reduce to sotorasib 120 mg QD in combination with RMC-4630 or discontinue treatment. During clinic visit days in C1, as well as D1 of subsequent cycles, sotorasib should be administered in the clinic in order to comply with blood PK, ctDNA, and ECG assessment timepoints.

[32]Blood samples (3 mL/sample) for RMC 4630 and sotorasib PK analyses will be obtained at the timepoints listed in Table 2.

[33]Blood samples (10 mL/sample) for ctDNA will be obtained at the timepoints listed in Table 2.

[34]For all subjects, archival tumor tissue collected preferably within 3 years should be submitted between screening and EOT. FFPE tissue blocks with sufficient specimen to allow sectioning for 21 × 4 micron slides are preferred. Alternatively, one H&E-stained slide with a 20 × 4 micron freshly cut specimen (with minimum 30% viable tumor volume) can be provided. Pretreatment fresh biopsies will be mandatory for subjects who do not have available archival tissue preferably from within 3 years, unless the investigator determines that the tumor site is not amenable to biopsy or poses a significant risk to subject safety. The Sponsor will evaluate this requirement on a case-by-case basis. The pre-treatment biopsy should not be collected until the subject is determined to be eligible for the study by the Sponsor. Any tumor site amenable to biopsy (excisional or needle [4 cores × 18 gauge or <18 gauge needle]) is acceptable, except for bone metastases. Acceptance of needle biopsy cores from >18-gauge needles will be evaluated by the Sponsor on a case-by-case basis and may require additional cores.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time; BIW = twice weekly; BUN = blood urea nitrogen; C = cycle; C1D1 (CxDx, etc) = Cycle 1 Day 1, etc; CPK = creatine phosphokinase; CR = complete response; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; D = day; ECG = electrocardiogram; eCRF = electronic Case Report Form; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOS = End-of-Study; EOT = End-of-Treatment; FFPE = formalin fixed paraffin embedded; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; GI = gastrointestinal; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; H&E = hematoxylin and eosin; HEENT = head, eyes, ears, nose, and throat; INR = international normalized ratio; $KRAS^{G12C}$ = *KRAS* with a mutation at codon 12, which encodes glycine (G) to cysteine (C); LVEF = left ventricular ejection fraction; MCH = mean corpuscular hemoglobin; MM = striated muscle; MRI = magnetic resonance imaging; MUGA = multigated acquisition; MCV = mean corpuscular volume; NSCLC = non–small-cell lung cancer; OCT = optical coherence tomography; PD-L1 = Programmed death-ligand 1; PET = positron emission tomography; PK =pharmacokinetics(s); PO = oral(ly); PR = partial response; PT = prothrombin time; PTT = partial thromboplastin time; QD = once daily; RBC = red blood cell; QTc = corrected QT interval; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; SAE = serious adverse event; SOC = standard-of-care; WBC = white blood cell.

Table 2: PK and [redacted] Sampling

Cycle/EOT Study Day	PK Time Points	[redacted] Time Points	Collection-Time Window
C1			
[redacted]	NA	[redacted]	NA
[redacted]	Predose	[redacted]	Within 1 hour before dose
	2 hours postdose	--	2 hours ±10 minutes after dose
C2, C3, C4			
[redacted]	Predose	[redacted]	Within 1 hour before dose
Every 3 cycles (C7, C10, C13, C16) afterward up to C16			
[redacted]	Predose	NA	Within 1 hour before dose
EOT	NA	X	Any time during visit
Extended-Use	NA	NA	NA

Abbreviations: C = cycle; [redacted]; EOT = End-of-Treatment; NA = not applicable; PK = pharmacokinetic(s).
Note: On any days that a PK specimen is collected, the subject should be administered study drug in the clinic.

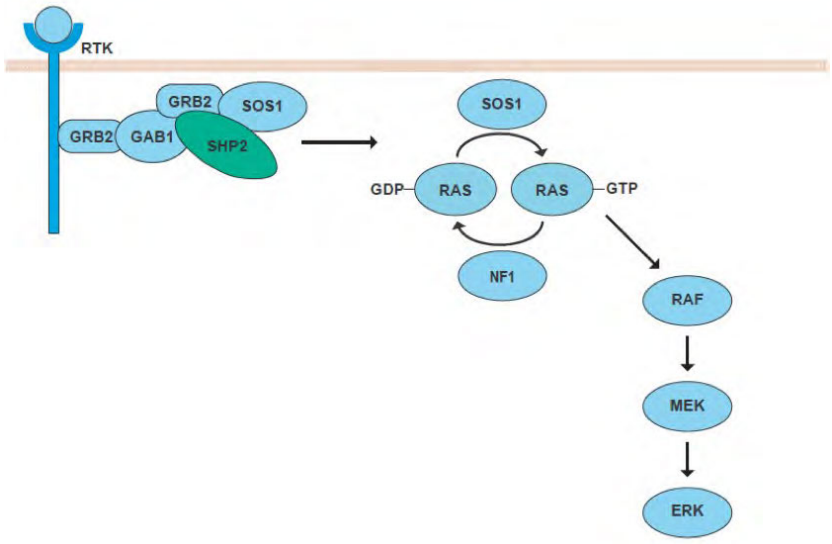
2. INTRODUCTION

2.1. Background

2.1.1. RMC-4630

SHP2 is a non-receptor protein tyrosine phosphatase and scaffold protein that functions downstream of multiple RTKs, integrating cell surface growth factor signals to promote RAS activation Figure 2. RMC-4630 was designed as a potent and selective SHP2 allosteric inhibitor that suppresses RAS activation and the proliferation in cancers that, distinct from those dependent on oncogenic RTKs, are driven by nucleotide cycling oncogenic point mutations (eg, $KRAS^{G12C}$) and wild-type amplification of *KRAS* and other RAS-GTP dependent downstream mutations, eg, $NF1^{LOF}$, or RAS-GTP dependent oncogenic *BRAF Class 3* (Wong, 2018; Fedele, 2018).

Figure 2: The RAS Signaling Pathway Demonstrating the Convergence Nodal Position of SHP2 in the Pathway



SHP2 is a convergent node for RTK to RAS signaling and regulator of RAS-GTP loading. SHP2 inhibition modulates RTK signal transduction as well as RAS signaling pathway hyperactivation driven by specific oncoproteins. Preclinical studies demonstrated that daily PO administration of RMC-4630 alone achieved dose-dependent tumor cytostasis, and in some instances, tumor reductions, in multiple CDX models bearing RAS signaling pathway activating mutations of interest: NSCLC NCI-H358 $KRAS^{G12C}$, pancreatic ductal adenocarcinoma (PDAC) MIA PaCa-2 $KRAS^{G12C}$, NSCLC NCI-H2122 $KRAS^{G12C}$, NSCLC NCI-H1838 $NF1^{LOF}$, and melanoma MeWo $NF1^{LOF}$ (Nichols, 2017; Nichols, 2018). RMC-4630 also significantly inhibited tumor growth in 2 PDX models of NSCLC in athymic nude mice: LUN#023 bearing *BRAF Class 3* ($BRAF^{D594N}$) and LUN#037, which carries $BRAF^{N581D}$, a known Class 3 variant position (see current RMC-4630 Investigator's Brochure [IB]).

RMC-4630 is a potent, selective, and orally bioavailable SHP2 allosteric inhibitor that is being developed for patients with tumors harboring certain activating genotypic aberrations in the RAS signaling pathway. In this study (Protocol RMC-4630-03), RMC-4630 will be studied in combination with sotorasib, a $KRAS^{G12C}$ inhibitor, in locally advanced or metastatic NSCLC

subjects with *KRAS*^{G12C} mutation after failure of prior standard therapy to determine the efficacy, safety, tolerability and PK profile of the combination.

Preclinical data demonstrate that the potency of *KRAS*^{G12C} inhibitor treatment can be modulated by upstream RTK activation (Lito, 2016), which occurs as an adaptive response to inhibition of *KRAS*^{G12C}OFF state with either sotorasib or adagrasib. Concurrent inhibition of RTK signaling can optimize RAS pathway signaling in *KRAS*^{G12C} tumors (Lito, 2016; Canon, 2019). The addition of a SHP2 inhibitor like RMC-4630 to *KRAS*^{G12C}OFF state inhibitors improves tumor responses in preclinical models (Hallin, 2020; Liu 2018) can also abrogate *KRAS* signaling, eliminate residual or bypass upstream RTK activity, and thereby lead to greater combinatorial efficacy as well as deeper and more durable responses.

Most patients with mutations/rearrangements that confer hyperactivation of the RAS signaling pathway have a poor prognosis. RMC-4630 is currently being studied in the clinic as a monotherapy and in combination with several agents, including cobimetinib (MEK inhibitor), pembrolizumab (checkpoint inhibitor), osimertinib (RTK inhibitor), and sotorasib (*KRAS*^{G12C}OFF state inhibitor). A first-in-human, Phase 1 dose-escalation and expansion study (RMC-4630-01; NCT03634982) established a recommended phase 2 dose (RP2D) and schedule (RP2DS) of [redacted] on a [redacted] schedule on 23 October 2020. As of 16November 2020, [redacted] subjects had been treated with RMC-4630 monotherapy. The median age reported for this subject population is 63 years (range: 24.0 to 86.0 years), median prior systemic therapies is 3 (range: 0 to 11) with 69% having received 3 or more prior systemic therapies. A majority (61.5% [64/104]) of enrolled subjects have an Eastern Cooperative Oncology Group (ECOG) score of 1. [redacted] Median treatment duration (range: 0 to 15.6 months). [redacted]. Therefore, the clinical activity observed in *KRAS*^{G12C} mutant NSCLC is encouraging and warrants further exploration in combination studies with *KRAS*^{G12C}OFF state inhibitors. As mentioned above, there is an ongoing study of RMC-4630 and sotorasib, which is also evaluating the safety and efficacy of this combination and is sponsored by Amgen.

RMC-4630 has been extensively evaluated in nonclinical studies to characterize its safety profile; the results of these studies support entry into clinical study. The following potential risks are based on emerging clinical data from the RMC-4630-01 (monotherapy) and RMC-4630-02 (combination) clinical trials: edema, diarrhea, anemia, and thrombocytopenia.

[redacted] More detailed information about the expected

benefits and risks and expected AEs of RMC-4630, based on clinical and preclinical data and drug class are in the current RMC-4630 IB, as well as in Section 2.2.1.

In summary, the preclinical and clinical findings reveal potential therapeutic approaches that use a potent SHP2 inhibitor in combination with another in-pathway inhibitor to counteract the evolution of resistance in tumors harboring alterations in the RAS signaling pathway. Additionally, the combination of SHP2 inhibition with sotorasib has the potential to provide therapeutic benefit in tumors driven by oncogenic mutations insensitive to either agent alone.

2.1.2. Sotorasib

Sotorasib (AMG 510) is a small molecule that specifically and irreversibly inhibits *KRAS*^{G12C} through a unique interaction with the P2 pocket-bound state (OFF state) by a mechanism similar to that described for other *KRAS*^{G12C} inhibitors (Lito, 2016). Preclinical studies showed that sotorasib inhibited nearly all detectable phosphorylation of extracellular signal-regulated kinase (ERK), a key downstream effector of *KRA*S, leading to durable complete tumor regression in mice bearing *KRA*S p.G12C tumors (Canon, 2019).

In a Phase 1 trial of sotorasib, subjects with advanced solid tumors (59 with NSCLC, 42 with CRC and 28 with other tumors) harboring the *KRAS*^{G12C} mutation received sotorasib QD (Hong, 2020). The subjects had received a median of 3 (range: 0 to 11) previous lines of anticancer therapies for metastatic disease. Objective response was assessed according to RECIST v1.1. Sotorasib showed encouraging anticancer activity. In the subgroup of subjects with NSCLC, 32.2% (19 subjects) had a confirmed objective response (CR or PR) and 88.1% (52 subjects) had disease control (objective response or stable disease [SD]); the median progression-free survival [PFS] was 6.3 months (range: 0.0+ to 14.9; + indicates that the value includes subject data that were censored at data cutoff). No dose-limiting toxic effects or treatment-related deaths were observed. Grade 3 or 4 treatment-related toxic effects occurred in 11.6% of the subjects.

On 28 May 2021, the US FDA granted accelerated approval to sotorasib for adult patients with *KRAS*^{G12C} mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy. The approval was based on CodeBreaK 100, a multicenter, single-arm, open label clinical trial (NCT03600883) that included subjects with locally advanced or metastatic NSCLC with *KRAS*^{G12C} mutations. Efficacy was evaluated in [redacted]ith at least one measurable lesion at baseline with disease progression after receiving an immune checkpoint inhibitor and/or platinum-based chemotherapy. Subjects received sotorasib 960 mg QD until disease progression or unacceptable toxicity. The major efficacy outcome measures were ORR according to RECIST v1.1, as evaluated by blinded independent central review and response duration (DOR). The ORR was 36% (95% CI: 28%, 45%) with a median response duration of 10 months (range 1.3+, 11.1). In a pooled Phase 1 and Phase 2 dataset of Amgen Study 20170543 for NSCLC at 960 mg (N=204), the most common adverse reactions (≥ 20% of subjects) were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. The most common laboratory abnormalities (≥ 25% of subjects) were decreased lymphocytes, decreased hemoglobin, increased AST, increased ALT, decreased calcium, increased ALP, increased urine protein, and decreased sodium. Serious adverse reactions occurred in 50% of subjects treated with sotorasib. Serious adverse reactions in ≥ 2% of subjects were pneumonia (8%), hepatotoxicity (3.4%), and diarrhea (2%). Fatal adverse reactions occurred in 3.4% of

subjects who received sotorasib due to respiratory failure (0.8%), pneumonitis (0.4%), cardiac arrest (0.4%), cardiac failure (0.4%), gastric ulcer (0.4%), and pneumonia (0.4%).

More detail regarding the potential risks, warning and precautions can be found in the current Sotorasib IB and in Section 2.2.1

2.1.3. RMC-4630 and Sotorasib Combination

Most patients with mutations/rearrangements that confer hyperactivation of the RAS signaling pathway have a poor prognosis. RMC-4630 is currently being studied in the clinic as a monotherapy and in combination with several agents, including cobimetinib (MEK inhibitor), pembrolizumab (checkpoint inhibitor), osimertinib (RTK inhibitor), and sotorasib (*KRAS*^{G12C}OFF state inhibitor).

The efficacy, safety, tolerability, and PK of the RMC-4630 and sotorasib combination in subjects with advanced solid tumors with *KRAS* p.G12C mutation is being evaluated in an ongoing Amgen-sponsored Phase 1b platform study (CodeBreaK 101C [NCT04185883]). CodeBreaK 101C was initiated in May 2020 and is currently dosing subjects with RMC-4630 at [redacted] of each week in a 21-day cycle (ie, Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle), after dose level review and clearance of two lower dose levels (RMC-4630 [redacted] of each week in a 21-day cycle (ie, Days 1, 4, 8, 11, 15, and 19 of each 21-day cycle) and [redacted] on [redacted] of each week in a 21-day cycle.

This protocol (RMC-4630-03) is designed to complement ongoing CodeBreaK 101C and will further characterize the efficacy, safety, tolerability, and PK of RMC-4630 and sotorasib combination therapy for subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC after failure of prior standard therapy. Early data (n=27) from CodeBreaK 101c with a median follow up of 5.8 months, show that combination of RMC-4630 and sotorasib appears to be safe and well tolerated. The most common study-treatment-related AEs of any grade in >10% of the population were edema (30%), diarrhoea (26%), dry mouth (11%), and fatigue (11%). Four subjects had treatment-related AEs leading to discontinuation of one or both study drugs and 12 subjects had a treatment-related AE leading to dose modification of one or both study drugs. Based on the PK profile, there were no drug-drug interactions between the study drugs. Among the subjects with NSCLC (n=11), the overall response rate was 27% overall and 50% in the sub-population of subjects who were KRAS^{G12C} inhibitor naïve (n=6). Durable partial responses were observed in 2 subjects who were KRAS^{G12C} inhibitor naïve and received 200 mg of RMC-4630 with 960 mg of sotorasib (Falchook, 2022).

Emerging clinical data from sotorasib monotherapy and adagrasib monotherapy suggest that *KRAS*^{G12C}-mutated NSCLC could represent a heterogenous population defined by comutations such as STK11 and KEAP1 (Li, 2021; Jänne, 2020). Preclinical data suggest SHP2 resistance in select tumors including those harboring *BRAF Class 1* and *2* and *NRAS* mutations (Nichols, 2018). Leveraging these learnings, this study will prospectively define analysis of sub-populations *KRAS*^{G12C}-mutated NSCLC without and with detectable comutations that might influence the outcome to sotorasib (eg, *STK11, KEAP1*) and/or RMC-4630 (eg, *BRAF*, *NRAS*).

More detailed information about the expected benefits and risks and expected AEs of RMC-4630, based on clinical and preclinical data and class of drugs are in the current RMC-4630 IB, as well as in Section 2.2.1.

The combination of SHP2 inhibition together with *KRAS*^{G12C}OFF state inhibition provides a potentially novel targeted treatment for patients with *KRAS*^{G12C} mutant NSCLC with relapsed or refractory solid tumors harboring mutations resulting in hyperactivation of the RAS signaling pathway.

More detailed information regarding the known and expected benefits, risks, and AEs of sotorasib is provide in the current Sotorasib IB.

2.2. Benefit/Risk Assessment

2.2.1. Overview and Potential Benefit

2.2.1.1. RMC-4630

RMC-4630 (also known as SAR442720 or RMC-0694630) is a potent, selective, orally bioavailable allosteric inhibitor of SHP2, a protein tyrosine phosphatase functioning downstream of multiple RTKs as a convergent node in RAS signaling. RMC-4630 is being developed primarily to combine with RAS inhibitors to treat RAS-addicted tumors. SHP2 also plays a vital role in promoting antitumor immunity and enhancing T-cells cytotoxic function. The current focus is to combine RMC-4630 with *KRAS*^{G12C} inhibitors as well as programmed cell death protein 1 (PD-1) inhibitors.

The current clinical development program for RMC-4630 comprises a Phase 1 monotherapy study RMC-4630-01 (NCT03634982) conducted by Revolution Medicines, a Phase 1b/2 combination study RMC-4630-02 (SHP2 inhibitor + mitogen activated protein kinase inhibitor; SHP2 inhibitor + epidermal growth factor RTK inhibitor; NCT03989115) also conducted by Revolution Medicines, and an Amgen sponsored Phase 1b study (CodeBreaK 101C; NCT04185883) evaluating RMC-4630 in combination with sotorasib in subjects with advanced solid tumors with *KRAS*^{G12C} mutation are ongoing. Sanofi is conducting a Phase 1/2 combination study TCD16210 (SHP2 inhibitor + programmed cell death-1 receptor inhibitor; NCT04418661). Please refer to the current RMC-4630 IB for a summary of the clinical development program.

In a Phase 1 monotherapy study, RMC-4630 demonstrated acceptable tolerability with an intermittent dosing schedule (Day 1 and Day 2 of each week) and single agent activity in subjects with *KRAS*^{G12C} NSCLC. Tumor and blood-based immune-oncology biomarkers demonstrated preliminary evidence of anti-tumor immune activation, supporting an immune-mediated mechanism of action for SHP2 in addition to modulation of RTK signal transduction.

2.2.1.2. Sotorasib

Sotorasib (AMG 510) is a small molecule that specifically and irreversibly inhibits *KRAS*^{G12C} through a unique interaction with the P2 pocket-bound state (OFF state) by a mechanism similar to that described for other *KRAS*^{G12C} inhibitors. Sotorasib is the first approved targeted therapy for tumors with *KRAS* mutation indicated for the treatment of adult patients with *KRAS*^{G12C} mutated locally advanced or metastatic NSCLC, marketed as LUMAKRAS™ or LUMYKRAS® in several countries.

2.2.1.3. Rationale for RMC-4630 in Combination with Sotorasib in Protocol RMC-4630-03

Most patients with mutations/rearrangements that confer hyperactivation of the RAS signaling pathway have a poor prognosis. Recent advances in the treatment paradigm for RAS mutant

NSCLC include several first-in-class irreversible inhibitors of *KRAS*^{G12C} (eg, sotorasib [AMG 510]) which have demonstrated a favorable safety profile along with early promising anti-tumor activity in subjects with advanced NSCLC harboring a *KRAS*^{G12C}. Recently, both (Canon, 2019; Hallin, 2020) have interrogated cellular mechanisms that limit the therapeutic response to these *KRAS*^{G12C} inhibitors, as a means to identify key vulnerabilities that can be co-targeted in combination with other therapeutic agents. Multiple lines of evidence indicate that baseline RTK activation, as well as adaptive resistance mechanisms that increase signaling flux downstream of RTKs, can limit therapeutic response to *KRAS*^{G12} inhibitors. Clustered regularly interspaced short palindromic repeats (CRISPR) based drug-anchored screens and combination experiments in vitro and in vivo have identified SHP2 as an important RAS/MAPK pathway node that can be co-targeted to enhance *KRAS*^{G12C} inhibitor activity and abrogate RTK-mediated adaptive resistance mechanisms.

Furthermore, nonclinical data demonstrates that the potency of *KRAS*^{G12C} inhibitors can be modulated by upstream RTK activation and concurrent inhibition of RTK signaling can lead to maximal *KRAS*^{G12C} inhibition. Tumor development in mutant *KRAS* driven murine models of NSCLC can be inhibited by genetic deletion of Ptpn11, the gene encoding SHP2, confirming the role of SHP2 as an important RAS/MAPK pathway node that can be co-targeted to enhance *KRAS*^{G12C} inhibitor activity and abrogate potential resistance via RTK activation. These published studies suggest that the addition of a SHP2 inhibitor like RMC-4630 to a targeted therapy against mutant *KRAS*^{G12C} may completely inhibit *KRAS* signaling, eliminate residual or bypass upstream RTK activity, and thereby promoting deeper and more durable responses.

This combination is also being tested in advanced *KRAS*^{G12C} mutant solid tumors including locally advanced or metastatic NSCLC in an ongoing Phase 1b study sponsored by Amgen (CodeBreaK 101C) within the US. The study consists of two parts, Part 1 dose exploration and Part 2 dose expansion. CodeBreaK 101C has tested and cleared all dose levels of RMC-4630, which include [redacted] of each week in a 21-day cycle, [redacted] 1D2 of each week in a 21-day cycle, and [redacted] of each week in a 21-day cycle in combination with [redacted] of sotorasib QD.

2.2.2. Important Risks

2.2.2.1. Identified and Potential Risks of RMC-4630

RMC-4630 is currently being evaluated as monotherapy and in multiple combination studies. The Phase 1, first-in-human study in adult subjects with relapsed/refractory solid tumors (NCT03634982) has established a RP2DS of [redacted] of each week in a 21-day cycle. The toxicity profile of RMC-4630 in humans is emerging and is provided in detail in the current RMC-4630 IB. Dose modification guidance for selected toxicities is provided in Section 6.7 and supportive care guidelines are provided in Section 6.7.1.

[redacted] Safety data, as of 17 July 2022, are summarized below.

[redacted]

of subjects in study RMC-4630-01.

The median time to first onset of a [redacted]

[redacted]

As of 17-Jul-2022, a total of [redacted] across the clinical development program had a reported event (irrespective of attribution to study drug(s)) consistent with [redacted] which include [redacted] with an [redacted] and 1 subject with an event of interstitial lung disease. Of the [redacted] with an event, 1 [redacted] received RMC-4630 monotherapy, while the remaining [redacted] received RMC-4630 in combination therapy (4 subjects with cobimetinib, 2 subjects with osimertinib, and 2 subjects with pembrolizumab). A total of 7 subjects had an event which was [redacted] which included [redacted] with a [redacted] (1 subject who received RMC-4630 with cobimetinib and 1 subject who received RMC-4630 with osimertinib).

In addition to the risks described above, thromboembolic events are being monitored. As of [redacted]

for subjects with [redacted]

Because full cytochrome P-450 (CYP) isoform phenotyping studies for RMC-4630 have not been completed, RMC-4630 remains a putative substrate of CYP3A4; precautions should be taken with co-administration of strong CYP3A4 inducers or inhibitors. These agents are contraindicated in this trial (see Appendix 8).

Based on published on-target effects from other small-molecule inhibitors of the RAS signaling pathway, including inhibitors of RTKs, and/or nonclinical toxicology studies with RMC-4630, the following toxicities (listed alphabetically) are possible: [redacted]. In general, toxicities are dose dependent and, in the case of MEK inhibitors, may also increase in frequency and severity with dosing duration.

In addition, the following toxicities listed alphabetically have been reported during clinical studies of more than one inhibitor of the RAS signaling pathway and it is not known whether they are on target toxicities: alopecia, conduction abnormalities, embryofetal toxicity, hand-foot-mouth syndrome, hyperglycemia, hypopigmentation, hypothyroidism, interstitial lung disease (ILD), left ventricular dysfunction/cardiomyopathy, neurotoxicity, and pleural effusions.

Additional supporting data from nonclinical studies are provided in the current RMC-4630 IB.

2.2.2.2. Potential Risks of Sotorasib

Based on non-clinical toxicity studies of sotorasib, the key safety information of sotorasib includes renal toxicity, anemia, leukocytosis, thyroid abnormalities, and splenomegaly. Based on clinical study data, the key risks to be monitored include increases to AST and ALT, and ILD/pneumonitis. Adverse drug reactions with the use of sotorasib include diarrhea, nausea, fatigue, vomiting, abdominal pain, increased liver enzymes, and pneumonitis. Clinical signs and symptoms of potential toxicities, along with safety laboratories, will be monitored during the study to ensure the subjects' safety. More detailed information about the safety profile and risks of sotorasib, including the most recent information on adverse drug reactions based on the ongoing clinical program, may be found in the current version of the Sotorasib IB.

2.2.2.3. Potential Risks of RMC-4630 and Sotorasib Combination

As sotorasib impacts signaling in the RAS-MAPK signaling pathway, it is possible that overlapping toxicities with RMC-4630 will be observed. The clinical study design builds in safeguards which minimize potential toxicities to subjects.

The combination of RMC-4630 and sotorasib has been previously administered in humans in an ongoing study conducted by Amgen (CodeBreaK 101C; NCT04185883). As stated above, CodeBreaK 101C is a Phase 1b study evaluating the safety, tolerability, pharmacokinetics, and efficacy of RMC-4630 in combination with sotorasib in subjects with previously treated $KRAS^{G12C}$ mutant advanced solid tumors. The combination of RMC-4630 and sotorasib has shown acceptable safety and tolerability to date, with no new safety signals. The risk of synergistic toxicity is anticipated to be low because sotorasib is highly selective for the $KRAS^{G12C}$ mutation, which has not been found in normal tissue. In general, if potential toxicities do occur, they are predicted to be dose and duration dependent, monitorable, and reversible. The nonclinical toxicity findings identified with RMC-4630 repeated daily dosing is largely similar to those described for sotorasib. When RMC-4630 and sotorasib are administered in combination, AEs (eg, diarrhea, hematological effects, renal effects, pneumonitis, hepatotoxicity, and QT

prolongation if co-administered with drugs known to prolong the QT interval) may increase in frequency and severity with duration of therapy and/or manifest at a lower individual dose of each treatment. Given the potential for overlapping toxicities in the combination therapy, subjects will be monitored by routine safety parameters as described in Section 2.2.2.4.

The potential of drug-drug interaction is low for RMC-4630 and sotorasib.

For more information, please see the risks associated with sotorasib (AMG 510) summarized in the current Sotorasib IB (Section 7) and the risks associated with RMC-4630 summarized in the current RMC-4630 IB (Section 7).

2.2.2.4. Steps to Minimize Risk

The RMC-4630-03 study will incorporate the following safety monitoring and risks mitigation strategies:

- Safety measures to minimize risks to subjects have been incorporated in the design of the study and eligibility criteria to specifically exclude subjects who may be at increased risk of specific toxicities
- Medications known to prolong QT are prohibited during study drug administration
- Guidance for investigators to follow institutional guidelines/standard of care with respect to implementation of prophylaxis for specific toxicities (eg, antibacterials for infections) to minimize risk to subjects
- The study will include a safety run-in period that will evaluate DLTs and clear a combination dose by the Dose Committee as guided by the mTPI-2 algorithm (see Appendix 11)
- In addition to DLT criteria, dose modifications after the DLT window have been included in order to reduce the risk of toxicity while continuing to provide subjects a potential treatment opportunity
- Safety monitoring (consisting of AE assessments, physical examinations, vital signs measurements, electrocardiograms [ECGs], clinical laboratory tests, ECOG performance status [PS], and echocardiogram [ECHO]/multigated acquisition [MUGA] scans), will occur at regular intervals throughout the study
- As a precaution, subjects receiving strong CYP3A4 inhibitors (see Appendix 8) and/or inducers are excluded, until further data become available
- Invasive measures in this study are limited to venipuncture (all study subjects) and tumor biopsies in subjects, when feasible. The primary purpose of the pretreatment biopsies is to assess tumor biology and explore predictive biomarkers (Hirsch, 2003) (see Section 8.7).
- An Internal Safety Monitoring Committee (ISMC) will be used to monitor the safety of RMC-4630 and sotorasib combination therapy throughout the study. The ISMC is RMC-4630-program specific and will review emergent safety data at regular intervals for all subjects during the trial in conjunction with data from other active RMC-4630 clinical trials. Additional details are provided in Section 8.3.6.2.

3. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are provided in Table 3.

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the antitumor effects of RMC-4630 and sotorasib in locally advanced or metastatic NSCLC subjects with *KRAS*^{G12C} mutation with and without co-existing genetic aberrations in specific genes such as *STK11/LKB1, KEAP1,* and *PIK3CA* (see detailed list in Appendix 9) after failure of prior standard therapy	ORR as assessed per RECIST v1.1
Secondary	
• To characterize the safety, tolerability, and PK of RMC-4630 in combination with sotorasib for subjects with *KRAS*^{G12C} mutant NSCLC after failure of prior standard therapy • To further characterize efficacy of RMC-4630 in combination with sotorasib as assessed by DOR, DCR, PFS, and OS in subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC after failure of prior standard therapy	• Incidence, nature, and severity of TEAEs, SAEs, clinically significant changes in laboratory tests, ECGs, and vital signs • Trough and approximate peak concentrations of RMC-4630 and sotorasib • DOR, DCR, and PFS as assessed per RECIST v1.1, and OS
Exploratory	
• To explore PK relationships with safety and/or efficacy endpoints • To investigate potential biomarkers by biochemical and/or genetic analysis of blood and/or tumor tissue samples	• Sotorasib and RMC-4630 exposure/safety and exposure/efficacy relationships • Quantification of biomarker expression (protein, RNA, and DNA levels) as appropriate in ctDNA and archival tumor tissues (or fresh, if archival tumor is not available).

Abbreviations: ctDNA = circulating tumor deoxyribonucleic acid; DCR = disease control rate; DNA = deoxyribonucleic acid; DOR = duration of response; ECG = electrocardiogram; *KRAS*^{G12C} = *KRAS* with a mutation at codon 12, which encodes glycine (G) to cysteine (C); NSCLC = non–small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; RNA = ribonucleic acid; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. STUDY DESIGN

4.1. Overall Study Design

This is a Phase 2 multicenter, open-label study evaluating the efficacy, safety, tolerability, and PK of RMC-4630 in combination with sotorasib in subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC who have received at least one prior systemic therapy. The overall study design schema is shown in Figure 1. The study will be conducted at approximately 40 clinical sites globally and is expected to enroll up to approximately [redacted].

Prior to enrollment, all subjects will undergo screening to determine study eligibility. The presence of *KRAS*^{G12C} mutation is required for enrollment. Eligibility will be assessed based on prior/local genomic testing using a clinically validated or qualified assay of tumor samples. Circulating tumor deoxyribonucleic acid (ctDNA) mutational analysis using a clinically qualified or validated test may also be used for enrollment.

Mutation testing results for all subjects must have occurred in a CLIA-/CAP-certified laboratory and collected preferably within 3 years of study enrollment. All local tumor genotyping analyses will be confirmed by central testing when the tumor tissue is provided. A fresh biopsy will not be used to determine eligibility.

This Phase 2 study will have a safety run-in period where RMC-4630 will be administered at a starting dose of [redacted] of each week in a 21-day cycle and sotorasib [redacted] QD in a 21-day cycle. Subjects will be evaluated for DLTs (see Section 8.4). The decision to escalate the RMC-4630 dose to [redacted] of each week in a 21-day cycle will be guided by a modified toxicity probability interval 2 (mTPI-2) algorithm (see Appendix 11) and made by the Dose Committee. After completion of the safety run-in (DLT clearance) of both dose levels, additional subjects may be enrolled into one or both dose levels for the purpose of dose optimization before selecting the final expansion dose. Expansion may commence as soon as the expansion dose has been selected from either CodeBreaK 101C or this study, whichever occurs first. The Sponsor may proceed directly to dose expansion without completing the safety run-in period. The combination dose for expansion will be determined by the Sponsor after taking into consideration the totality of available data from CodeBreaK 101C and the cumulative data from this study. The study will enroll a total of approximately [redacted] globally. Subjects will be categorized into one of two cohorts:

- Cohort 1 will be the primary cohort of this study and will consist of *KRAS*^{G12C} NSCLC subjects **without** potential genetic aberrations in specific genes, such as *STK11/LKB1, KEAP1*, and *PIK3CA* (see detailed list in Appendix 9).
- Cohort 2 will consist of *KRAS*^{G12C} NSCLC subjects **with** co-existing genetic aberrations in specific genes, such as *STK11/LKB1, KEAP1*, and *PIK3CA* (see detailed list in Appendix 9).

4.1.1. Duration of Treatment

Subjects will be permitted to remain on study treatment until disease progression per RECIST v1.1, unacceptable toxicity, or other criteria for withdrawal are met (see Section 7.1, whichever occurs first. Subjects who discontinue treatment will return to the clinical site for an EOT visit within 30 days after last dose of study treatment. Subjects who are benefitting from

study treatment at the time of the EOS may continue treatment in the Extended-Use phase of the study.

4.1.2. Long-Term Follow-Up Period

For subjects in the main study who discontinue treatment and do not withdraw consent, there will be a LTFU period for clinical evaluation of disease status and survival. Survival follow up will be discontinued for subjects currently in LTFU at the time of the initiation of the Extended-Use phase. See Section 7.2 for details.

4.1.3. Duration of the Study

The main study duration is approximately 2 years. The Extended-Use phase will be conducted through June 2024.

4.1.4. Intervention After the End of the Study

Subjects who are on treatment at the EOS and are deriving clinical benefit from RMC-4630 and sotorasib may be considered for enrollment in a separate Extended-Use phase of the study. These subjects should enter the separate Extended-Use phase without interruption of treatment and should complete EOT assessments listed in the SoA (Table 1) prior to treatment on Day 1 of the Extended-Use phase. Assessments outlined in the SoA are to be followed during the Extended-Use phase of the study.

4.2. Scientific Rationale for Study Design

This is a Phase 2 study designed to characterize the efficacy, safety, tolerability, and PK of RMC-4630 and sotorasib combination therapy in subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC after failure of prior standard therapy. The PK (trough and approximate peak concentrations) and efficacy (ORR, DOR, and PFS assessed per RECIST v1.1) endpoints in this study are commonly used for PK modeling and characterization of exposure/safety and exposure/efficacy relationships for the target population of subjects with *KRAS*^{G12C} mutant NSCLC.

4.3. Dose Justification

4.3.1. RMC-4630

RMC-4630 is being studied in the clinic as a monotherapy in Study RMC-4630-01 (NCT03634982), and in various other combination studies. RMC-4630 has been tested at various dose levels and schedules including daily dosing, intermittent dosing schedule on [redacted] and [redacted] As of 16 November 2020, [redacted] have been treated with RMC-4630 monotherapy; the RP2DS was determined to be [redacted] of each week in a 21-day cycle. At this dose level, the plasma concentrations of RMC-4630 were above those predicted to be clinically active, based on preclinical models. The C_{max} reached, and often exceeded, the apoptotic threshold (75% effective concentration [EC_{75}]), defined as plasma concentrations that were associated with induction of tumor regressions or cell death in preclinical models. Trough concentrations at the end of each week were close to the 50% effective concentration (EC_{50}) for RAS signaling pathway inhibition in tumors, which was predicted to be sufficient to permit normal tissue recovery and therefore contribute to tolerability.

Furthermore, RMC-4630 and sotorasib combination is being tested in an ongoing Amgen-sponsored Phase 1b platform (CodeBreaK 101C). CodeBreaK 101C was initiated in May

2020 and is currently dosing subjects at RMC-4630 [redacted] of each week in a 21-day cycle and [redacted] of each week in a 21-day cycle). This Phase 2 study (RMC-4630-03) will have a safety run-in period in which RMC-4630 will be administered at [redacted] of each week in a 21-day cycle as the starting dose with the option of escalating to RMC-4630 [redacted] of each week in a 21-day cycle if tolerated per modified toxicity probability interval 2 (m-TPI2).

4.3.2. Sotorasib

The FDA-approved dose for sotorasib monotherapy in patients with *KRAS*^{G12C} mutated locally advanced or metastatic NSCLC is 960 mg QD administered PO. Therefore, the same dose will be used for this study. The Sponsor notes that the US FDA expressed concerns regarding the validity of 960 mg to be the optimal dose of sotorasib due to the following reasons (CDER application #214665Orig1s000 sotorasib; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214665Orig1s000MultidisciplineR.pdf [accessed 28 May 2021]): 1) No relationship between dose and drug exposure at steady-state, 2) no evidence of dose-response relationship, 3) gastrointestinal toxicities are lower at the lower doses tested in dose escalation, 4) preclinical data suggest that the minimal effective dose is [redacted] daily, and 5) the labeled dose requires patients to take eight tablets at a time, which is a pill-burden on patients. Upon approval of LUMAKRAS, the US FDA has requested that Amgen compare their approved 960 mg dose with a 240 mg dose, as one of their postmarketing requirements. Data readout from a postmarketing study of sotorasib dose optimization in patients with advanced NSCLC who have received one prior therapy (see https://clinicaltrials.gov/ct2/show/NCT03600883) is imminent at the time of this protocol amendment. If supported by the data, at the Sponsor's discretion and after discussion with the Dose Committee, new subjects enrolling on this trial may be treated at the lower sotorasib dose of 240 mg in combination with RMC-4630 (see Table 4 and Table 5). Subjects currently enrolled at 960 mg may continue at their current dose or dose reduce based on discussion with the Sponsor's Medical Monitor. Subjects developing toxicities at sotorasib 240 mg QD may dose reduce to sotorasib 120 mg QD or discontinue treatment.

4.4. EOS Definition

The main study duration is approximately 2 years. The EOS is defined as the date of LSLV or 12 months after the last subject receives the first dose of study treatment, whichever occurs first. Subjects who are benefitting from study treatment may continue receiving treatment through the Extended-Use phase of the study (Section 4.1.3).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

All subjects must meet ALL of the following inclusion criteria to be admitted into the study:

1. Subject must be ≥18 years of age at the time of signing the ICF.
2. Subject is capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
3. Subject must have pathologically documented, locally advanced or metastatic *KRAS*^{G12C} NSCLC (not amenable to curative surgery) that has progressed on prior standard therapies **(no more than 3 prior lines of therapies are allowed**), as follows:
    a. Subject with actionable oncogenic driver mutations (eg, epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase [ALK], and reactive oxygen species proto-oncogene 1 [ROS1]) must have received standard-of-care anticancer treatments, including approved drugs for oncogenic drivers in their tumor type.
    b. Subject's tumor must harbor a *KRAS*^{G12C} mutation assessed by a CLIA-/CAP-certified laboratory or equivalent per region.
    c. Subjects with locally advanced *KRAS*^{G12C} NSCLC must have received prior radio-chemotherapy followed by immunotherapy (applicable only in France)
4. Subject must have measurable disease per RECIST v1.1, criteria.
5. Subject must have a life expectancy of at least 3 months.
6. The subject's ECOG PS of 0 to 1 with no deterioration in PS at 2 weeks prior to C1D1. Rescreening is required if PS is >1 for any reason prior to C1D1.
7. Subject must have the ability to typically ingest and retain PO medications.
8. Subject must have adequate hematological and biological function, as follows:
    a. Bone marrow function
        i. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L without use of hematopoietic growth factors
        ii. Hemoglobin ≥9 g/dL; subject must not have received a red blood cell (RBC) transfusion within 28 days of Screening
        iii. Platelets ≥100 × 10^9/L; subject must not have received a platelet transfusion within 14 days of Screening
    b. Subject must have hepatic function as follows:
        i. AST and ALT ≤2.5 × upper limit of normal (ULN)
        ii. Bilirubin ≤1.5 × ULN (<2.0 × ULN for subject with documented Gilbert's syndrome or <3.0 × ULN for subject for whom the indirect bilirubin level suggests an extrahepatic source of elevation)

c. Subject must have renal function as follows:
Serum creatinine ≤1.5 × ULN and creatinine clearance (CrCl) of >50 mL/min (using the Cockcroft-Gault formula or 24-hour urine collection)

d. Subject must have coagulation function as follows:
Prothrombin time (PT)/international normalized ratio (INR) and activated partial thromboplastin time (aPTT)/partial thromboplastin time (PTT) <1.3 × ULN, or within target range if taking prophylactic anticoagulant(s)

9. Female subject is eligible to participate if she meets the following criteria:
   a. Is not a woman of childbearing potential (WOCBP), OR
   b. Is a WOCBP and using a contraceptive method that is highly effective (ie, with a failure rate of <1% per year), preferably with low user dependency, during the treatment period and for at least 2 months after the last dose of study treatment and agree not to donate eggs (ie, ova and oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment. Hormonal contraception efficacy may potentially be decreased due to interaction with sotorasib; therefore, male condoms must be used in addition to any hormonal-based contraception methods.
10. Male subject is eligible to participate if he agrees to the following during the treatment period and for ≥3 months after the last dose of study treatment:
    a. Refrains from donating sperm (any donation of sperm should be conducted prior to study start)
    b. PLUS, either:
    c. Abstain from intercourse as his preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent, OR
    d. Must agree to use a male condom AND should also be advised of the benefit for a nonpregnant female partner to use a highly effective method of contraception as a condom may break or leak
11. Subject must provide unstained, archived, tumor tissue samples collected preferably within the past 3 years. Subjects who do not have archived tissue available are required to undergo a tumor biopsy. Subjects who neither have archival tumor tissue samples nor can provide fresh pretreatment biopsies may still be eligible to participate in the study with approval from the Sponsor Medical Monitor.

5.2. Exclusion Criteria

If a subject meets **ANY** of the following criteria, he or she will be excluded from study participation:

1. Subject has primary central nervous system (CNS) tumor(s)
2. Subject has known or suspected leptomeningeal or brain metastases or spinal cord compression. However, subjects who were previously treated for these conditions who have had stable CNS disease (no evidence of clinical and radiographic disease progression and asymptomatic in the absence of corticosteroids or anti-convulsant

therapy) are eligible to participate in the study, as long as SD is documented by a brain magnetic resonance imaging (MRI) performed within 28 days of C1D1.

3. Subject who has any of the following cardiac abnormalities:
    a. Medically uncontrolled hypertension (≥160 mmHg systolic blood pressure or ≥100 mm Hg diastolic blood pressure)
    b. Congestive heart failure Class ≥2, as defined by the New York Heart Association
    c. Acute coronary syndrome (including unstable angina, coronary artery stenting, or angioplasty, bypass grafting within prior 6 months); myocardial infarction within 6 months of informed consent.
    d. History or evidence of current, uncontrolled, clinically significant, unstable arrhythmias
        i. Subject with medically controlled atrial fibrillation >1 month prior to Study Day 1 is eligible.
        ii. Subject who has a pacemaker in place to control atrial arrhythmias is a candidate for the study.
    e. History of congenital long QT syndrome or prolonged corrected QT interval (QTc) >470 msec for females and > 450 msec for males using Fridericia's formula (unless a pacemaker is in place) or uncorrectable abnormalities in serum electrolytes (ie, sodium, potassium, calcium, magnesium, phosphorus):
        i. Subject may use average of triplicate readings for assessing QTc interval.
        ii. Subject with an implantable defibrillator is not eligible to participate in the study.
    f. Current cardiomyopathy or history within in the past 12 months prior to informed consent.
    g. Baseline left ventricular ejection fraction (LVEF) below the institutional lower limit of normal (LLN) or <50%, whichever is lower.
4. Any prior history of (or active) ILD or pneumonitis, or prior thoracic radiotherapy within 2 months of enrollment.
5. Subject has a history of or ongoing retinal pigment epithelial detachment (RPED), central serous retinopathy, or retinal vein occlusion (RVO), or predisposing factors to RPED or RVO (eg, uncontrolled glaucoma or ocular hypertension, uncontrolled diabetes mellitus, hyperviscosity, or hypercoagulability syndromes; see Section 8.2.8 for details).
6. *Former exclusion criterion is withdrawn.*
7. Subject has of Grade ≥2 proteinuria.
8. Subject has a history of cerebrovascular accident or transient ischemic attack within previous 6 months of signing the informed consent form (ICF).
9. Subject has a known activating SHP2 mutation (eg, Noonan syndrome).
10. Subject has an active autoimmune disease requiring systemic treatment (ie, with use of disease modifying agents, non-physiologic doses of corticosteroids, or

immunosuppressive drugs) within the past 2 years of signing the ICF; includes current autoimmune sequelae or previous Grade >2 autoimmune sequelae from checkpoint inhibitors or other immunomodulatory treatments that require systemic therapy. Subject with autoimmune endocrine disorder on hormonal supplementation may be enrolled, even if Grade >2 upon initial presentation, if approved by the Medical Monitor.

11. Subject has known human immunodeficiency virus (HIV) infection.
12. Subject has an active/chronic hepatitis B or C virus infection.
13. Subject has a known impairment of gastrointestinal (GI) function that may significantly alter the absorption of RMC-4630 (eg, uncontrolled nausea and vomiting, diarrhea, malabsorption syndrome, inflammatory bowel disease, gastrectomy, or small bowel resection).
14. Subject has a history of severe allergic reactions to any of the study treatment components.
15. Subject has major surgical procedures ≤28 days or non-study-related minor procedures ≤7 days prior to Cycle 1 Day 1 (C1D1); in all cases, the subject must be sufficiently recovered and stable before treatment administration.
16. Subject has any other unstable or clinically significant concurrent medical condition (including, but not limited to substance abuse, uncontrolled intercurrent illness such as active infection, arterial thrombosis, or symptomatic pulmonary embolism) that would, in the opinion of the investigator, jeopardize the safety of a subject, impact their expected survival through the end of the study participation, and/or impact their ability to comply with the protocol. Any subject who had a pulmonary embolism within 3 months of C1D1 will also be excluded.
17. Subject has had prior therapy with one or both of the following agents, meets criteria for exclusion:
    a. *KRAS*^{G12C} inhibitor
    b. SHP2 inhibitor
18. Subject has had treatment with chemotherapy or biologics/monoclonal antibodies <21 days or 5 half-lives (whichever is shorter) before C1D1.
19. Subject has had treatment with non-thoracic radiation therapy <14 days before C1D1.
20. Subject has had treatment with tyrosine kinase inhibitor (TKI), hormonal therapy (except megesterol acetate) <7 days before C1D1.
21. Subject has had treatment with immunotherapy (eg, checkpoint inhibitors) 14 to 21 days before C1D1, depending on cycle length of drug.
22. Subject has had treatment with all other anticancer treatments including investigational agents that do not fit in the above categories <21 days before C1D1.
23. Use of proton pump inhibitors (PPIs) within 3 days or H2 receptor antagonists (H2-blockers) within 1 day prior to study intervention. Subjects using an antacid or other acid reducing agent must have a 24-hour wash out period prior to initiation of study treatment.

24. Subject has had consumption of strong CYP3A4 inducers or inhibitors within 7 days prior to initiation of study treatment and requires treatment with strong CYP3A4 inducers or inhibitors.
25. Subject has had consumption of strong P-glycoprotein (P-gp) inhibitors (eg, cyclosporine, tacrolimus) within 7 days prior to initiation of study treatment and requires treatment with a strong P-gp inhibitor.
26. Use of known CYP3A4 and P-gp sensitive substrates (with a narrow therapeutic window), within 14 days or 5 half-lives of the drug prior to study day 1 that was not reviewed and approved by the principal investigator.
27. Subject has had clinically significant reversible toxicities from prior cancer therapy that have not recovered to Grade 1 or baseline, except for alopecia.

    Subject with Grade ≤2 neuropathies due to prior treatment will be allowed on study. Subject with other Grades ≤2 clinical nonsignificant toxicities, may be allowed on study after discussion with Medical Monitor.
28. Female who is pregnant or breastfeeding.
29. Unwillingness or inability to comply with the protocol.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Subjects should refrain from consumption of grapefruit or grapefruit-containing products, or Seville oranges from 7 days before the start of study treatment until after the final dose.

Fasting (except water) 1 hour prior to and 1 hour after each RMC-4630 dose is required. Fasting is **NOT** required for sotorasib; however, on days when both medications are taken together, fasting is requisite due to the requirements of RMC-4630. Sotorasib tablets should be swallowed whole, with or without food.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently able to receive treatment in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (ie, screen failure) may be rescreened within 5 days of the initial screening date of screen failure. Rescreened subjects should be assigned the same subject number as for the initial screening. Only hematology, chemistry, and coagulation tests may need to be repeated if outside the screening window. Other clinical testing will not need to be repeated if outside screening window (ie, within 5 days).

6. STUDY TREATMENT

6.1. Study Treatments Administered: RMC-4630 and Sotorasib

The study treatment for this protocol is combination therapy of the investigational drug product RMC-4630 and the marketed product sotorasib.

RMC-4630 [redacted] will be administered PO on [redacted] of each week in a 21-day cycle (ie, Days 1, 2, 8, 9, 15, and 16 of each 21-day cycle). RMC-4630 capsules should not be crushed or chewed.

Sotorasib [redacted] mg will be administered PO QD per instructions provided in the current Sotorasib IB. At the Sponsor's discretion, new subjects enrolling on this trial may be treated at sotorasib 240 mg in combination with RMC-4630 (see Table 4). Subjects currently enrolled at sotorasib 960 mg may continue at their current dose or dose reduce based on discussion with the Sponsor Medical Monitor. Subjects developing toxicities at sotorasib [redacted] may dose reduce to sotorasib [redacted] or discontinue treatment.

For the main protocol, the subject should administer the study treatment at approximately the same time every day except for clinic visit days as listed in the SoA (Table 1). On these clinic visits, the subject should await instruction from the study staff to coordinate with the timing of PK and/or biomarker sampling.

Subjects deriving benefit from treatment who enter the Extended-Use phase of the study should continue treatment without interruption.

Table 4: Study Treatment Administered: RMC-4630 and Sotorasib

Component Name	Drug Product Information
Treatment Name	RMC-4630 and sotorasib combination therapy
Type	Drugs
Dose Formulation	RMC-4630: PIC drug product Sotorasib: tablet
Unit Dose Strengths	RMC-4630: [redacted] g Sotorasib: 120 mg
Dosage Levels	RMC-4630: [redacted] for a treatment cycle of 21 days Sotorasib: [redacted] QD
Route of Administration	PO with water after 1 hour fast; no food or drink (other than water) allowed for 1 hour after administration for RMC-4630 alone or RMC-4630 in combination with sotorasib. PO; no restrictions on food for sotorasib when taken alone.
Investigational Product	RMC-4630 in combination with Sotorasib IMP to be supplied for all sites unlabeled drug product sourced from Amgen

Table 4: Study Treatment Administered: RMC-4630 and Sotorasib (Continued)

Component Name	Drug Product Information
Sourcing	RMC-4630: Manufactured and provided centrally by the Sponsor through the third party CMO Sotorasib: IMP (unlabeled drug product supplied by Amgen) to be provided by Sponsor
Packaging and Labeling	RMC-4630: Study treatment (PIC drug products) is packaged in 8-count HDPE bottles with open label. Sotorasib: IMP (unlabeled drug product supplied by Amgen) to be provided for all sites
Current/Former Name(s) or Alias	RMC-4630, RMC-0694630 Sotorasib: AMG 510

Abbreviations: CMO = contract manufacturing organization; HDPE = high-density polyethylene; IMP = investigational medicinal product; PIC = powder-in-capsule; PO = oral(ly); QD = daily; US = United States.

6.2. Preparation/Handling/Storage/Accountability

RMC-4630 (powder in capsule [PIC] drug products: 20 mg and 100 mg, respectively) are packaged in high density-polyethylene (HDPE) bottles with open labeling and are shipped and stored below 30°C (86°F) but they are not to be frozen.

Clinical sotorasib 120 mg tablets are yellow, oblong-shaped, film-coated, debossed with “AMG” on one side and “120” on the opposite side. Sotorasib tablets are packaged in 120-count HDPE bottles.

Sotorasib is stored at 20°C to 25°C (68°F to 77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F).

The sotorasib tablets supplied by Amgen will be clinically labeled and QP released as IMP and distributed to the site by the Sponsor.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive RMC-4630 and sotorasib as a combination and only authorized site staff may supply study treatment to the subjects.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the study Pharmacy and Investigational Product Administration Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, nonrandomized study. In order to minimize bias, subjects will be assigned sequentially as they are enrolled into the study using the inclusion and exclusion criteria outlined in Section 5.1 and Section 5.2, respectively. Enrollment will be confirmed by the Sponsor Medical Monitor after review of all supporting documentation for eligibility criteria. Subjects

will be assigned a screening number at the time of signing the ICF. If a subject is a screen failure, the number will not be reassigned.

For Italy only, the eligibility form will not be used to allow the Sponsor or contract research organization (CRO) to make any medical decisions for the subject. Instead, it will be used for Sponsor and CRO to confirm that the subject's eligibility check has been fully completed (eg, no inclusion/exclusion criteria are missing, and all of the screening procedures have been completed), with the intention to ensure subject safety and data integrity.

6.4. Study Treatment Compliance

6.4.1. Compliance Instructions

Dosing instructions will be provided to the subject, and subject compliance with study treatment will be reviewed at each visit. Compliance will be assessed by counting returned RMC-4630 capsules, in conjunction with subject diary information and subject questioning. Subject compliance for sotorasib administration will only be assessed by reviewing subjects' diaries and questions asked during clinic visits. The investigator should follow the guidance provided in Section 8.5 if a subject is suspected to have taken greater than the assigned dosage.

6.4.2. Missed Dose

RMC-4630: If a subject misses a Day 1 (D1) dose of RMC-4630, it should be taken as soon as the missed dose is discovered. The D2 dose should then follow 24-hours after. If the subject misses D2 dose, it should be taken as soon as the missed dose is discovered, provided there is at least a 24-hour gap between D1 dose and D2 dose. If the gap between D1 and D2 dose is more than 48 hours, the D2 dose should not be administered and should be recorded as an omission. The subject should not administer more than the recommended dose.

Sotorasib: If a dose of sotorasib is missed, or if vomiting occurs when the dose is taken, the subject should resume dosing with the next scheduled dose.

6.5. Permitted Concomitant Therapy

Supportive care (eg, antiemetics, analgesics, blood transfusions, hematopoietic growth factor support) may be used at the investigator's discretion and in accordance with institutional procedures. Localized radiotherapy used for palliative purposes may be considered after discussion with the Medical Monitor. Anticoagulation with low-dose aspirin, low-molecular weight heparin (LMWH), and direct Factor-Xa inhibitors are allowed. Contraceptives are also allowed throughout the study (see Section 5.1).

If an acid reducing agent cannot be avoided, administer sotorasib and RMC-4630 either 4 hours before or 10 hours after a local antacid.

Avoid coadministration with CYP3A4 substrates for which minimal concentration changes may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, adjust the substrate dosage in accordance with the current Sotorasib IB.

Avoid coadministration with P-gp substrates for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the substrate dosage in accordance with the current Sotorasib IB.

A local antacid (eg, calcium carbonate, sodium bicarbonate, or bismuth subsalicylate-containing agents such as Tums, Alka-Seltzer, Pepto-Bismol, etc.) may be permitted after discussion with the Sponsor Medical Monitor if RMC-4630 is administered either 4 hours before or 10 hours after the local antacid.

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the subject is receiving at the time of enrollment or receives during the study, must be recorded along with the following:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6. Prohibited Concomitant Therapy

In addition to prohibited medications/foods listed in the Exclusion Criteria (Section 5.2), a complete list of prohibited medications during study treatment is provided in Appendix 8.

The following medications are prohibited while on study treatment:

- PPIs and H2-blockers
- Medications known to prolong QTc interval
- Anti-cancer therapy (except study treatment medications)
- Strong CYP3A4 inhibitors and inducers
- Strong P-gp inhibitors
- Known CYP3A4 and P-gp sensitive substrates (with a narrow therapeutic index), that were not reviewed and approved by the principal investigator

6.7. Dose Modification

A 21-day cycle will be maintained, and dose interruption will be noted in the 21-day cycle schedule. Two types of dose modifications are allowed: dose interruption and dose level reduction. Any allowed dose modification and any deviation from the intended dose (missed doses or overdoses due to subject error) should be documented on the dose electronic Case Report Form (eCRF).

In general, dose adjustments should be based on attribution to a particular treatment. Certain AEs are known to be associated with administration of sotorasib (see current Sotorasib IB), whereas others have been observed with the administration of RMC-4630 in clinical or preclinical studies (see current RMC-4630 IB). However, because both components of the study treatment affect the RAS signaling pathway, overlapping toxicities are likely to be observed.

If RMC-4630 is discontinued due to toxicity, sotorasib monotherapy can be continued as it is the standard-of-care in this patient population. However, if sotorasib is discontinued due to toxicity

reasons, RMC-4630 continuation as monotherapy may be considered, provided that the subject per investigator discretion is clinically benefitting from treatment with no evidence of disease progression (and approval by the Sponsor's Medical Monitor).

Depending on the RMC-4630 starting-dose level, up to 2 dose-level reductions for [redacted] and one dose-level reduction for the [redacted] are permitted for upon discussion with the Sponsor Medical Monitor. Depending on the sotorasib starting-dose level, up to 2 dose-level reductions for 960 mg and one dose-level reduction for 240 mg are permitted upon discussion with the Sponsor's Medical Monitor. Guidance for dose reduction for both components of the study treatment is presented in Table 5. If more than 2 dose reductions are required for either RMC-4630 or sotorasib 960 mg, or more than one dose reduction is required for sotorasib 240 mg, administration must be discontinued for that component and treatment with the remaining single component (RMC-4630 or sotorasib) may be considered, depending on investigator assessment of clinical benefit and discussion with the Sponsor's Medical Monitor. Dose modification guidelines for a subset of common AEs seen with RMC-4630 and/or sotorasib (per the current Sotorasib IB) are shown in Table 6. General guidance for dose modification is presented in Table 7. The investigator or treating physician should use his/her best medical judgement for management.

When reducing dose, the dose of one or both agents (RMC-4630 and sotorasib) could be reduced depending on which may be causing the toxicity.

Table 5: Dose Reduction Guidelines with RMC-4630 and Sotorasib

Dose Level	Treatment and Dosage		
	RMC-4630 ([redacted] in a 21-Day Cycle)	Sotorasib (QD)	
1 (subject starting dose level)[1]	[redacted]	960 mg	240 mg
-1 (dose reduction from starting dose for either component of study treatment if needed)	[redacted]	480 mg	120 mg
-2 (dose reduction from starting dose for either component of study treatment if needed)	[redacted]	240 mg	NA

Abbreviations: [redacted]; NA = not applicable; QD = once daily.

[1] Starting dose level represents the subject's assigned dose level at enrollment. For example, if the subject enrolled at the RMC-4630 140 mg dose level (default starting dose), they would dose reduce to 100 mg. A subject enrolled at the RMC-4630 200 mg dose level would dose reduce to 140 mg, followed by reduction to 100 mg as necessary.

Table 6: Dose Modification Guidelines for RMC-4630 and Sotorasib

AE	Action
Thrombocytopenia	**Thrombocytopenia associated with clinically significant bleeding, at any level:** Hold RMC-4630 and sotorasib and follow hemorrhage recommendations. **Uncomplicated thrombocytopenia (without clinically significant bleeding):** **Grade 1-2:** Continue treatment at current dose level for both components of study treatment and monitor closely. **Grade 3-4:** Manage per institutional guidelines and interrupt RMC-4630 dosing until the event recovers to Grade 1 or within normal limits or returns to baseline. If recovery occurs, resume RMC-4630 at one dose level lower. If Grade 3-4 events recur, hold dose until recovery to Grade 1 or within normal limits or returns to baseline and a second dose reduction may be considered. If the subject continues to experience high-grade thrombocytopenia, RMC-4630 may be discontinued permanently and sotorasib monotherapy can be continued. **Subjects on anticoagulant(s)** Subjects receiving anticoagulant therapy should be monitored closely for evidence of treatment-emergent thrombocytopenia. Subjects who develop treatment-emergent thrombocytopenia may need to be managed more conservatively, due to increased risk of bleeding.
Neutropenia/ Febrile Neutropenia/ Anemia/ Pancytopenia	Assess for other causes. Hold concomitant medications associated with myelosuppression. **Grade 3 neutropenia**: Hold RMC-4630 if clinically indicated until the event recovers to Grade 1 or within normal limits or returns to baseline. If improvement occurs within 3 weeks, restart RMC-4630 at one dose level lower. If there is no improvement within 3 weeks, or upon recurrence of Grade 3 neutropenia, additional dose reduction of RMC-4630 or permanent discontinuation of RMC-4630 can be considered. **Grade 3 febrile neutropenia**: Hold RMC-4630 and sotorasib until fever resolves and ANC recovers to Grade 1 or is within normal limits or returns to baseline. If improvement occurs within 2 weeks, restart RMC-4630 one dose level lower. If there is no improvement within 2 weeks, discontinue RMC-4630 and sotorasib. **Grade 3 anemia**: Assess transfusion history. Transfuse per institutional guidelines. Hold RMC-4630 if clinically indicated until the event recovers to Grade 1 or within normal limits or returns to baseline. If improvement occurs within 4 weeks, restart RMC-4630 at the same dose level. If the AE re-occurs, consider dose reduction to one dose level lower for RMC-4630 after the AE resolves to Grade 1 or within normal limits or returns to baseline. If the AE does not improve within 4 weeks, consider discontinuation of RMC-4630. **Grade 4 pancytopenia**: Hold RMC-4630 and sotorasib until resolves to Grade 1, within normal limits or returns to baseline. If improvement occurs within 4 weeks, restart RMC 4630 and sotorasib one dose level lower. If there is no improvement within 4 weeks, discontinue both drugs.

Table 6: Dose Modification Guidelines for RMC-4630 and Sotorasib (Continued)

AE	Action
Rash	**Grade 1-2 (tolerable)**: Administer supportive care and continue study treatment. **Grade 3 or 4**: Hold both components of study treatment until improvement to ≤ Grade 2. If there is improvement to ≤ Grade 2 within 3 weeks, then reduce RMC-4630 by 1 dose level. If recurs, a second dose reduction for RMC-4630 and/or a dose reduction for sotorasib may be considered. If rash continues to occur with 2 dose reductions of RMC-4630 and/or 1 dose reduction of sotorasib, consider permanent discontinuation of RMC-4630. If Grade 3-4 rash does not improve within 3 weeks, permanently discontinue RMC-4630. **Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN):** Any grade, permanently discontinue both components of study treatment
Ocular symptoms	**For neurosensory retinal detachment and other ocular events:** **Grade 3 or 4** – Hold RMC-4630 until the AE recovers to normal or Grade 1 and re-start RMC-4630 at one dose level lower. For recurrence of a Grade 3 AE, dose interrupt until the AE recovers to normal or Grade 1 and consider a second dose reduction for RMC-4630. Permanently discontinue RMC-4630 if the Grade 3 AE re-occurs after two dose reductions of RMC-4630. For recurrence of a Grade 4 AE, permanently discontinue RMC-4630. Discontinue RMC-4630 for any grade AE of retinal vein occlusion (RVO).
Hemorrhage	Rule out other causes. **Grade 1-2:** Continue both components of study treatment at the current doses and monitor closely for signs or symptoms of clinically significant bleeding. **Grade 3:** Hold RMC-4630 until resolution. If the event resolves within 3 weeks, consider restarting RMC-4630 at a lower dose. If not resolved within 3 weeks, permanently discontinue RMC-4630. **Grade 4 or CNS hemorrhage**: If hemorrhage is associated with thrombocytopenia or reduced platelet count from baseline, permanently discontinue RMC-4630. If not, hold RMC-4630 until resolution, and restart at a lower dose if resolves within 3 weeks. If not resolved within 3 weeks, permanently discontinue RMC-4630.
Diarrhea/ Nausea/ Vomiting	**Grade 1-2:** Maximal supportive care. Continue both components of study treatment at current doses and ongoing prophylaxis maybe considered upon investigator's discretion after the first event **Grade 3**: Hold both components of study treatment (if receiving maximal supportive care) until the event recovers to Grade 1 or normal or returns to baseline. If improves within 3 weeks, then restart RMC-4630 and sotorasib at 1 dose level lower. If not resolved within 3 weeks, permanently discontinue RMC-4630. If event recurs, hold both components of study treatment and consider a second dose reduction for both components of study treatment or permanent discontinuation of one or both components of study treatment depending on the clinical benefit. Note: Only one dose reduction is applicable for subjects starting dosing at 240 mg of sotorasib. **Grade 4:** Permanently discontinue RMC-4630 and sotorasib for Grade 4 diarrhea or vomiting

Table 6: Dose Modification Guidelines for RMC-4630 and Sotorasib (Continued)

AE	Action
Liver function tests (AST, ALT, and/or total bilirubin)	**Grade 1:** Continue both components of study treatment at current doses. **Grade 2 AST or ALT with symptoms OR Grade 3 to 4 AST or ALT elevation**: Rule out other causes such as metastatic liver disease, concomitant drugs, infection, hepatitis etc. Hold both RMC-4630 and sotorasib until the event recovers to Grade 1 or within normal limits or returns to baseline, then dose reduce RMC-4630 and sotorasib to one dose level lower. If AE does not improve or recurs, dose reduce another dose level. No dose modification is required for isolated elevations of GGT. Note: Only one dose reduction is applicable for subjects starting dosing at 240 mg of sotorasib. Both components of study treatment should be permanently discontinued for concurrent elevation of AST or ALT >3 × ULN **AND** total bilirubin >2 × ULN or INR >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe DILI (potential Hy's law case). If liver injury is due to other causes such as viral hepatitis, acute liver disease, or another drug capable of liver injury, evaluate the extent of liver injury (eg, albumin level, PTT, INR, etc) and if considered to be severe, either consider continuing at a lower dose for both components of study treatment or discontinue one or both components of study treatment.
Hypertension	**Grade 2:** Treat according to institutional/provider guidelines in accordance with goal of reduction to Grade 1 or baseline. Continue RMC-4630 and sotorasib. **Grade 3:** Treat according to institutional guidelines with the goal of reducing blood pressure to Grade 1 or within normal limits or baseline. Consider holding RMC-4630. If there is improvement, restart RMC-4630 at the same dose level or one dose level lower per investigator judgement. **Grade 4:** Treat according to institutional guidelines. Permanently discontinue RMC-4630.
ILD / pneumonitis	Any Grade Withhold RMC-4630 and sotorasib if ILD/pneumonitis is suspected. If diagnosis is confirmed, permanently discontinue sotorasib and RMC-4630.

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug-induced liver injury; GGT = gamma-glutamyl transferase; ILD = interstitial lung disease; INR = international normalized ratio; PTT = partial thromboplastin time; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

Table 7: General Dose Modification Guidelines with RMC-4630 and Sotorasib for All Other AEs

Severity Grade	Action
Grade 1	Continue both components of study treatment at the current dose
Grade 2	May continue both components of study treatment without dose interruption and manage the toxicity using institutional guidelines. Dose interruption may be considered for one component of study treatment if the toxicity is a suspected toxicity of RMC-4630 and/or sotorasib, respectively. Upon recovery to baseline or Grade 1, treatment may be restarted at the same dose. If the toxicity re-occurs, consider a dose reduction for one of the components of study treatment if a causal relationship to the AE is suspected with RMC-4630 and/or sotorasib, respectively.
Grade 3	Hold treatment with both components of study treatment until recovery to normal or baseline or Grade 1 and manage per institutional guidelines. Upon recovery, subject may start RMC-4630 and sotorasib at one dose level lower. If AE re-occurs after one dose reduction, consider a second dose reduction for one or both components of study treatment. Note: Only one dose reduction is applicable for subjects starting dosing at 240 mg of sotorasib. If permanent discontinuation of either component of study treatment is being considered in the setting of re-occurrence of the AEs, RMC-4630 should be discontinued prior to sotorasib.
Grade 4	Hold treatment with both components of study treatment until recovery to normal or baseline or Grade 1 and manage per institutional guidelines. Upon recovery, a causal relationship should be carefully evaluated with RMC-4630 and permanent discontinuation of RMC-4630 considered for certain Grade 4 AEs. If it decided to continue treatment with RMC-4630, it should be at a reduced dose level. Sotorasib may be continued at one dose level lower upon recovery. If event re-occurs after sotorasib dose reduction and RMC-4630 reduction/discontinuation, consider permanent discontinuation of sotorasib.

Abbreviations: AE = adverse event.

6.7.1. Supportive Care Guidelines for Selected Expected Toxicities

Dose modification guidelines for RMC-4630 and sotorasib are summarized in Table 6 and Table 7. Toxicities known from the administration of sotorasib can be found in the current Sotorasib IB. In general, AEs should be managed per institutional guidelines, if available, and should include evaluation for all potential underlying causes. Appropriate subspecialty consultation should be sought, as clinically indicated. The investigator or treating physician should use his/her best medical judgement for management. Guidelines for selected toxicities are summarized below.

6.7.2. Management of Rash

For cutaneous changes suspicious of erythema multiforme or Stevens-Johnson syndrome (SJS), hold all study interventions, treat as per institutional guidelines, and consider dermatology consultation.

For maculopapular rash or perifollicular eruptions, emollients alone may be used for Grade 1 AEs. For Grade 2 AEs, addition of antihistamines and/or topical corticosteroids and/or oral minocycline or doxycycline may be considered. For Grade >2 events, oral steroids may be required.

For dry skin, alcohol-free emollients and soap substitutes should be considered. For folliculitis or cysts, soap substitutes and topical or oral antibiotics are recommended. Consider surgical excision for symptomatic, uninfected cysts. For an erythema-nodosum type rash, emollients, topical steroids, and analgesics are recommended. In more severe cases, dermatologic evaluation, and systemic steroids and/or may be required.

Consultation with a dermatologist should be considered as clinically indicated, including worsening or refractory symptoms, or rapidly growing lesions.

6.7.3. Management of Diarrhea

Evaluate for other or concomitant causes, including medications (eg, stool softeners, laxatives, antacids), infection, including *Clostridium difficile*, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber.

Premedication for management of diarrhea will be allowed after, but not before, the first dose of study treatment. Premedication should be administered as directed by the investigator.

For Grade 1 or 2 diarrhea, dietary modifications should be considered, including cessation of lactose-containing products, eating small meals, and adequately hydrating. Consumption of the banana, rice, apples, and toast (BRAT) diet may be helpful. In addition, loperamide or codeine may be used or alternatives in refractory cases, such as octreotide and budesonide.

For ≥ Grade 3 diarrhea, consider hospitalization for fluid and electrolyte replacement and antibiotics, particularly if accompanied by fever or Grades 3-4 neutropenia.

Consultation with a gastroenterologist should be considered, particularly for severe or refractory cases.

6.7.4. Management of Ophthalmologic Complications

The causal relationship between a change in vision and the study treatment should be carefully explored and an ophthalmologist should be consulted. Immediate consultation should be sought for Grade >1 visual changes. Special attention should be given to macular findings (with optical coherence tomography [OCT] utilization) or retinal vein abnormalities (eg, RVO). If consultation cannot be obtained within 7 days of onset, interrupt all study interventions until the consultation has occurred.

If RVO is diagnosed, permanently discontinue study treatment immediately and treat per institutional guidelines. If uveitis is diagnosed, withhold study treatment, and consider use of topical steroids until resolution. If central serous retinopathy or neurosensory retinal detachment is diagnosed, withhold all study interventions until symptoms resolve and retinal exam shows resolution.

There were no reported cases of retinopathy in RMC-4630-01. However, symptoms of retinopathy were observed in 6.7% (7/104) of subjects, of whom one experienced photopsia and 6 experienced blurred vision. Therefore, subjects treated with RMC-4630 should be monitored for retinopathy. Symptoms include blurred vision, altered color perception, shadows, light sensitivity, metamorphopsia, and glare. Ophthalmic examination by best corrected visual acuity (BCVA), pinhole vision, and OCT are key (refer to Common Terminology Criteria for Adverse Events [CTCAE], v5.0, for grading; note that the grades are based on BCVA).

The onset of retinopathy may occur very soon after dosing (eg, hours to weeks), and may also resolve spontaneously over time. For significant declines in visual acuity, dose hold according to Table 6 until improvement, then restart at the next lower dose level. Ophthalmology (eg, retinal specialist) consultation should be considered, if clinically indicated.

6.7.5. Management of Hypertension

Early identification and treatment of hypertension is recommended. Evaluate for other or concomitant causes. Assess renal function as well as urinalysis. For recurrent or persistent Grade 2 hypertension (systolic blood pressure 140-159 mm Hg or diastolic blood pressure 90-99 mm Hg) treat according to institutional guidelines with the goal of therapy to reduce blood pressure to £ Grade 1. Hypertension associated with life-threatening consequences (eg, malignant hypertension, neurological deficits, hypertensive crisis), permanently discontinue study treatment. Provide supportive care per institutional guidelines.

Cardiology or nephrology consultation should be considered, as clinically indicated.

6.7.6. Management of Liver Function Abnormalities and Hepatotoxicity

Monitor liver function tests (LFTs, which include ALT, AST, and total bilirubin) prior to the start of the study, weekly during Cycle 1, Day 1 and Day 15 during Cycle 2, Day 1 every Cycle starting at Cycle 3, and at EOT/EOS or as clinically indicated, with more frequent testing in subjects who develop transaminase and/or bilirubin elevations. Assess whether metastatic disease to the liver is contributing to liver function abnormalities and/or hepatotoxicity. Evaluate for infections or other causes of increased liver function abnormalities if appropriate. Consider imaging of the liver. Concomitant medications that may potentiate hepatotoxicity or metabolized by the liver should be held or reduced and the extent of liver injury should be evaluated (eg, albumin level, PTT, or INR).

Concurrent elevation of AST or ALT >3 × ULN **AND** total bilirubin >2 × ULN or INR >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe drug-induced liver injury (DILI) (possible Hy's law case). Study Treatment should be permanently discontinued.

If liver injury is due to other causes such as viral hepatitis, acute liver disease, or another drug capable of liver injury, evaluate the extent of liver injury (eg, albumin level, PTT, INR, etc) and if considered to be severe, either consider a lower dose for both components of study treatment or discontinue one or both components of study treatment.

Hepatology consultation should be considered, as clinically indicated.

6.7.7. Management of Hemorrhage

Evaluate complete blood count (CBC) and coagulation laboratories. Transfuse blood products and correct coagulation abnormalities as per institutional guidelines. Hold all study interventions if hemorrhage associated with thrombocytopenia, reduced platelet count from baseline, or at the discretion of investigator.

6.7.8. Management of Fatigue

Other causes of fatigue should be evaluated (eg, infection, disease progression and hematological, electrolyte, and endocrine abnormalities). Dose-modification and/or low-dose corticosteroids may be considered. General guidelines from Table 7 can be used to manage fatigue as it may be an overlapping toxicity for both RMC-4630 and sotorasib.

6.7.9. Pneumonitis

Respiratory symptoms such as dyspnea, cough, shortness of breath, etc, should be investigated with a chest X-ray or chest computed tomography (CT) scan. Evaluate for possible infections and other causes of respiratory compromise including progressive pulmonary disease, cardiac dysfunction, or any environmental factors, etc.

If the diagnosis of ILD or pneumonitis is confirmed, permanently discontinue sotorasib and RMC-4630. Initiate treatment per investigator judgement with corticosteroids and supportive care as per institutional guidelines.

6.7.10. Management of Fluid Retention/Overload Events

Evaluate for other or concomitant causes including medications. Treat according to institutional guidelines including the cessation of other medications known to be associated with the development of fluid retention/overload events, if clinically indicated. General guidelines from Table 7 can be used to manage fluid retention/overload events as it is considered to be an overlapping toxicity for both RMC-4630 and sotorasib.

7. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

In some instances, it may be necessary for a subject to permanently discontinue study treatment. Refer to the SoA (Table 1) for data to be collected at the time of discontinuation of study treatment.

Subjects must stop study treatment, but continue to be monitored in the study, under the following circumstances:

- Subject experiences a Grade 4 AE and is deemed by the investigator not to meet the criteria for withdrawal from the study (see Section 7.2).
- Subject experiences prolonged QT interval corrected using Fridericia's formula (QTcF); prolonged QTcF is defined as >500 msec **OR** change from baseline >60 msec that does not resolve after excluding other causes.

A subject must be discontinued from protocol-prescribed treatment if any of the following apply:

- Documented disease progression, based on RECIST v1.1; in certain circumstances (eg, an isolated site of progression with responses at other sites that may be amenable to localized radiotherapy), subjects may be allowed to continue therapy during and after radiation with approval from Sponsor Medical Monitor.
- Unacceptable toxicity
- Subject's request to withdraw from study treatment or withdraw of consent
- Ineligibility
- Unwillingness or inability to comply with study requirements
- Initiation of alternative anticancer therapy
- Investigator's decision
  - Clinical need for concomitant or other ancillary therapy that is not permitted in the study
  - Unrelated intercurrent illness that, in the judgment of the investigator, will affect assessments of clinical status to a significant degree
  - Investigator believes that it is in the best interest of the subject to withdraw from the study
- Pregnancy
- Lost to follow-up
- Sponsor's decision to terminate the study

Subjects who discontinue study treatment should complete the EOT visit, within 30 days after the last treatment dose. Subjects currently in LTFU should discontinue follow-up. See Section 7.2 for details on study discontinuation.

7.2. Subject Discontinuation/Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. These withdrawals are expected to be uncommon.

A subject may be withdrawn from the study for any of the following reasons:

- Subject's withdrawal of consent for participation in the study
- Sponsor's decision to terminate the study
- Subject is lost to follow-up
- Death

Upon permanent discontinuation of study treatment for any reason, including for subjects in the Extended-Use Phase, an end-of-treatment (EOT) visit should be completed within 30 days after the last dose of study treatment or before any new antitumor treatment is started.

Following the EOT visit, subjects will be considered to have completed the study. Survival follow up will be discontinued for subjects currently in LTFU.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request in writing destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and determine whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address, or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.
  Study discontinuation at specific sites or of the study as a whole are described in Appendix 1 (Study and Site Closures).

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be used for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each subject over approximately 9 months (13- to 14-cycle study duration), including any extra assessments that may be required, will not exceed 0.9 L. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Subjects will be assessed for response using RECIST v1.1 (see Appendix 6), as assessed by the investigator. All measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Measurable disease is required for each subject (Inclusion Criterion 3 [Section 5.1]). Response assessments will be assessed by the investigator based on physical examination (including measurement of cutaneous lesions) and CT scans or MRI. Imaging should include chest and abdomen (depending on primary tumor type, site of metastasis and investigator assessment). At the investigator's discretion, the imaging studies may be repeated at any time if disease progression is suspected. Additional studies, such as positron emission tomography (PET) or bone scans, should be performed if clinically indicated. Care should be taken to repeat the same modality used at screening throughout the study and to ensure all anatomy imaged at screening is again imaged at follow-up scans for any given subject. As part of the tumor assessment, physical examinations should include all areas of tumor involvement that are amenable to examination, including biopsy sites, lymph nodes, and bone tenderness, if applicable.

All imaging studies should be evaluated by a local radiologist with expertise in the imaging modality. The investigator is responsible for determining the overall response at each timepoint.

Radiological imaging and tumor assessments are required at screening and every 2 cycles starting from Cycle 3 (ie, every 6 weeks [±1 week]) up to Cycle 9, every 4 cycles (ie, every 12 weeks [±1 week]) thereafter and EOT. Radiographic response (CR and PR) requires

confirmation by a repeat scan at least 4 weeks after the first documentation of response and may be delayed until the next scheduled scan to avoid unnecessary procedures.

In the Extended-Use phase of the study, tumor imaging is not required per protocol. If required, imaging should be performed according to local standards of care and may be entered in the eCRF at the end of the extended use phase, if available.

8.2. Safety Assessments

Subjects will undergo the following safety assessments listed below and described in the following sections. Planned time points for all safety assessments are provided in the SoA (Table 1). Refer to the column on safety assessments for the Extended-Use phase of the study (Table 1) AEs, SAEs (Section 8.3)

- Hematology, clinical chemistry, liver transaminases and bilirubin tests (Section 8.2.6), coagulation tests (PT, INR, and aPTT or PTT) and urinalysis.
- Vital signs (Section 8.2.2)
- Body weight and height (Section 8.2.3)
- Physical examination (Section 8.2.1)
- 12-lead ECGs (Section 8.2.4)
- ECHO/MUGA scans (Section 8.2.5)
- Ophthalmologic examinations (Section 8.2.8)
- Concomitant medications/procedures
- ECOG performance status (Section 8.2.7)

The ISMC will review emergent safety data from the RMC-4630 program at regular intervals for all subjects during the trial in conjunction with data from other active RMC-4630 studies, described in Section 8.3.6.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, and throat (HEENT), dermatologic, cardiovascular, respiratory, GI (including assessments of liver and spleen), musculoskeletal, neurological, and lymphatic systems. Height and weight will also be measured and recorded. A symptom/AE directed physical examination should be performed as indicated by subject presentation or subject-reported symptoms or AEs.
- A limited examination should include an evaluation of the HEENT, dermatologic, cardiovascular, respiratory, and GI systems. A symptom/AE directed physical examination should be performed as indicated by subject presentation or subject-reported symptoms or AEs.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Vital signs will be measured, preferably in a seated position, after an approximately 5-minute rest. Vital signs will include temperature, systolic and diastolic blood pressure, pulse rate, pulse oximetry, and respiratory rate. Results should be recorded on the appropriate eCRF. In the Extended-Use phase, vital signs results will be recorded in subject's medical record.

8.2.3. Weight and Height

Weight should be measured throughout the study as indicated in the SoA (Table 1). Coats and shoes should be removed prior to measurement. Height should be measured at screening, without shoes.

8.2.4. Electrocardiograms

The 12-lead ECGs will be obtained as outlined in the SoA (Table 1) for all subjects using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and QTcF intervals. Refer to Section 7.1 for QTcF withdrawal criteria. Additional QTcF readings or continuous monitoring should be obtained to demonstrate improvement or resolution as per institutional guidelines. Subjects should be in the supine position after several minutes of inactivity before any study-related ECGs are conducted.

The ECGs can be evaluated by the Investigator and/or by a local cardiologist for a final assessment, and these results should be recorded in the eCRF. An evaluation by a cardiologist will not be required for routine follow-up of ECGs and will be at the discretion of the Principal Investigator/Sub-Investigator. However, evaluation by a cardiologist will be required if the subject experiences a cardiac AE/SAE or if the subject experiences a QTc/QTcF prolongation.

A single 12-lead ECG should be performed at Screening. The average of triplicate readings for assessing QTc interval may be used at Screening to determine eligibility. Triplicate 12-lead ECGs should be obtained on C1D1 and C1D15 predose and approximately 2 to 4 hours post-dose. Then a single pre-dose ECG should be obtained on D1 of every 2 cycles starting at C3 (eg, C3D1, C5D1, etc) and at EOT (see SoA [Table 1] for full schedule).

8.2.5. Echocardiograms/Multigated Acquisition Scans

All subjects must have their LVEF assessed by two-dimensional ECHO scan or MUGA scan as part of the screening procedure and as outlined in the SoA (Table 1). If a subject does not complete 2 cycles of study treatment, the EOT assessment for LVEF is not required, unless clinical signs or symptoms warrant additional imaging.

ECHO is the preferred method since it can detect wall motion abnormalities. However, in situations where an ECHO machine is not readily available or is technically limited, a MUGA scan may be obtained to evaluate LVEF. The same methodology should be used throughout the study and, to the greatest extent possible, at the same institution/facility.

The LVEF is to be calculated based on institutional guidelines and must be within institutional normal limits or 50%, whichever is lower, before a subject can enroll into the study. The LLN for the LVEF at the institution/facility should be recorded on the respective eCRF along with the LVEF result.

8.2.6. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Table 1) for the timing and frequency.
- The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment to current study therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. Refer to Appendix 2 for additional information pertaining to reporting of potential Hy's Law cases.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study after the first dose of study treatment until EOT should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified where possible, and the Sponsor notified.
  - All protocol required- laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA (Table 1).
  - If laboratory values from non–protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the eCRF.

8.2.7. ECOG Performance Status

ECOG performance status (Appendix 7) should be evaluated by the investigator by direct questioning of the subject at screening and at timepoints delineated in the SoA (Table 1).

8.2.8. Ophthalmologic Examinations

Ophthalmic examination if clinically indicated (ie, if subject is at high risk for RVO, RPED, and/or central serous retinopathy because of predisposing factors [uncontrolled glaucoma or ocular hypertension, uncontrolled diabetes mellitus, hyperviscosity, or hypercoagulability syndromes]), including full fundoscopic examination and OCT should be performed at Screening by an ophthalmologist as described in the SoA (Table 1). Additional examinations should be performed during study treatment as clinically indicated.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

Monitoring and recording of AEs and SAEs will be conducted throughout the study. After the signing of the ICF, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated treatment will be collected (eg, SAEs related to invasive procedures, such as biopsies or medication washout). Any medical occurrence that begins before the start of study treatment but after obtaining informed consent, and which is not considered an SAE caused by a protocol-mandated treatment, will be recorded on the Medical History/Current Medical Conditions Section of the eCRF rather than the AE section.

All AEs and SAEs will be collected from the start of treatment until 30 days after the last dose, or upon initiation of alternative cancer treatment, whichever occurs first. After this period, investigators should report only SAEs that are thought to be related to RMC-4630 and/or sotorasib.

Any SAE that is determined to be study-treatment related (possibly, probably, or definitely related) will be followed to resolution or stabilization, until it is determined to be irreversible by the investigator, the subject is lost to follow-up, or it has been determined that the study treatment is not the cause of the AE/SAE, whichever occurs first. After this period, investigators should report only SAEs that are thought to be related to RMC-4630 and/or sotorasib.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of investigator awareness, as indicated in Appendix 3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. During the Extended-Use phase of the study, only SAEs (irrespective of causality) and related AEs will be reported in the EDC. All SAEs will also be reported on the SAE Report Form.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.3.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts through the last study visit. All AEs (regardless of relationship to study treatment) and SAEs determined not to be study-treatment related (ie, not related and unlikely related) will be followed through the last study visit and be noted as “continuing” if not resolved at this visit.

All SAEs considered study-treatment related (possibly, probably, or definitely related) will be followed until resolution, stabilization, is determined to be irreversible by the investigator, the subject is lost to follow-up (as defined in Section 7.3), or it has been determined that the study

treatment is not the cause of the AE/SAE, whichever occurs first. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. During the Extended-Use phase of the study, only SAEs (irrespective of causality) and related AEs will be reported in the EDC. All SAEs will also be reported on the SAE Report Form. Reporting of AEs/SAEs will end after the subject initiates alternative cancer treatment.

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification (ie, within 24 hours of becoming aware of the event) by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to expeditiously notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, central IRBs/IECs, and investigators.
- The Sponsor will prepare investigator safety reports for suspected unexpected serious adverse reactions (SUSARs), according to local regulatory and local IRB/IEC requirements and Sponsor policy, and forward them to investigators, as necessary within 7 calendar days for Fatal and Life-Threatening SUSARs and 15 calendar days for all other SUSARs.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the RMC-4630 IB and will notify the IRB/IEC, if appropriate, according to local requirements.
- The Sponsor will regularly monitor reporting of SUSARs through compliance metrics and corrective and preventative actions to ensure that all recipients receive SUSAR reports in a timely manner.
- During the Extended-Use phase of the study, only SAEs (irrespective of causality) and related AEs will be reported in the EDC. All SAEs will also be reported on the SAE Report Form.

8.3.5. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects who become pregnant will be collected after the start of study treatment and will be followed to determine the outcome of the 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 4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

- Pregnancy reporting as detailed above will continue during the Extended-Use phase of the study and should be reported to Drug Safety on the SAE report form.

8.3.6. Committees

8.3.6.1. Dose Committee

The Dose Committee is a study specific committee, composed of Sponsor representatives and investigators. Additional details regarding memberships, roles, and responsibilities are provided in the Dose Committee Charter.

The Dose Committee will evaluate the safety data for the safety lead-in portion of the study. The combination dose for the expansion phase of the study will be decided by the Sponsor after taking into consideration the totality of data from both CodeBreaK 101C and the cumulative data from this study. The Sponsor may proceed directly to dose expansion in this study without completing the safety run-in period based on review of available data.

8.3.6.2. ISMC

The ISMC consists of representatives from the Sponsor and the designated CROs, as outlined in the ISMC Charter. The ISMC will review emergent safety data as per the ISMC charter from the RMC-4630 program after approximately every 3 months or after the first 6 subjects have completed 2 cycles in this study, whichever is earlier. The ISMC may also perform emergent ad hoc reviews of the safety data for all subjects during the study. Subsequently the committee will review data approximately every 3 months. The committee may adjust the timing of the review from the defined schedule, depending on the rate of enrollment. The committee will consist of the medical monitor, and a biostatistician. Relevant findings from the safety data reviews will be discussed with the study investigators. Based on the ongoing safety assessments, the committee may recommend changes in dosing regimen or other alterations to study procedures. The medical monitor may convene a meeting sooner should any concerns arise from review of data or from the investigators.

8.4. Dose Limiting Toxicity Criteria

Potential DLTs are defined as all AEs specified below that occur during the first cycle of study treatment and that are considered by the investigator to be related to RMC-4630 and/or sotorasib.

DLT criteria are outlined below as follows:

- An AE that results in permanent discontinuation of RMC-4630 or sotorasib
- An AE that results in a delay of > 2 weeks in the start of Cycle 2
- Febrile neutropenia
- Grade 4 neutropenia of any duration
- Grade 3 neutropenia lasting >7 days
- Grade 3 thrombocytopenia with Grade ≥2 bleeding
- Grade 4 thrombocytopenia
- Grade 4 anemia
- Grade ≥4 vomiting and diarrhea

- Grade 3 vomiting or diarrhea lasting >3 days despite optimal medical support
- Grade ≥3 nausea lasting 3 days or more, despite optimal medical support
- Grade ≥3 rash lasting 3 days or more despite optimal medical support
- Grade 3 AST or ALT elevation lasting >5 days or Grade ≥4 AST or ALT elevation of any duration
- Grade ≥3 bilirubin elevation
- Grade ≥3 QTc prolongation
- Retinal vein occlusion
- Any other Grade ≥3 AE with the following exceptions:
  - Grade 3 Fatigue lasting 7 days or less
  - Asymptomatic Grade 3 electrolyte abnormalities that last <72 hours, are not clinically complicated, and resolve spontaneously or respond to medical interventions
  - Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
  - Other select laboratory abnormalities that do not appear to be clinically relevant or harmful to the subject and/or can be corrected with replacement or modifications (eg, Grade 3 lymphopenia, Grade 3 hypoalbuminemia)
- Any subject meeting the criteria for a Hy's Law case (ie, severe DILI) will be considered a DLT. A Hy's Law case is defined as the following: AST or ALT values of ≥3 × ULN, AND total bilirubin >2 × ULN or INR >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other preexisting or acute liver disease, or another drug capable of the observed injury), to explain the observed liver related laboratory abnormalities.

If a subject experiences a DLT during the DLT evaluation period during Cycle 1 of the safety run-in period, sotorasib and/or RMC-4630 treatment should be modified according to Table 6 and Table 7.

8.5. Treatment of Overdose

For this study, any dose of RMC-4630 or sotorasib that is greater than the intended dose per administration or 2 administrations at the intended dose or more of sotorasib within <12 hours (QD dosing) or 2 administrations of RMC-4630 <12 hours apart (BIW D1, D2 dosing) will be considered an overdose. There is no clinical experience with an overdose of RMC-4630 in human clinical trials. No experiments have been performed to determine whether the effects of an overdose can be reversed, and there are no known antidotes.

Revolution Medicines does not recommend specific treatment for an overdose. The individual should be monitored clinically, and supportive care should be undertaken as clinically indicated.

In the event of an overdose, the investigator should:

1. Halt the dispensation and administration of the involved medication. The investigator may also hold the second medication based on his/her clinical judgement.
2. Contact the Medical Monitor immediately.
3. Closely monitor the subject for any AE/SAE, ECG, and laboratory abnormalities (blood glucose, liver function tests, creatinine, blood urea nitrogen (BUN), creatine phosphokinase (CPK), and complete blood count) until RMC-4630 and/or sotorasib can no longer be detected systemically.
4. Obtain a plasma sample for PK analysis within 1 to 2 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis). Note, the PK sample collection applies to the main protocol only and not the Extended-Use phase.
5. Document the quantity as well as the duration of the overdose in the eCRF.
6. Decisions regarding resumption of study treatment will be made by the investigator in consultation with the Sponsor's Medical Monitor based on clinical evaluation of the subject.

8.6. Pharmacokinetics

Plasma samples will be obtained for PK analysis of RMC-4630 and sotorasib as outlined in the SoA and (Table 2). Peripheral blood samples will be collected within C1 for sparse PK testing, and additional PK evaluations will continue to be obtained through C4 and every 3 cycles afterward up to Cycle 16. Note, PK sample collection applies to the main protocol only and not the Extended-Use phase.

PK parameters (ie, approximate peak and trough concentrations) of RMC-4630 and sotorasib will be assessed for each evaluable subject:

- Whole blood samples of approximately 3.0 mL will be drawn and processed into plasma for measurement of plasma RMC4630 and sotorasib concentrations as specified in the -SoA and Table 2. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock) of each sample will be recorded.
- Samples will be used to evaluate the PKs of RMC-4630 and sotorasib. Each plasma sample will be divided into 4 aliquots (2 each for primary and backup). Samples collected for analyses of plasma RMC-4630 and sotorasib concentrations may also be used for exploratory analysis, such as analysis of plasma RMC-4630 and sotorasib metabolites.

Genetic analyses will not be performed on these plasma samples. Subject confidentiality must be maintained. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF. There will be no PK sample collection in the Extended-Use phase of the study.

8.7. Tumor Genetics

Enrollment will be determined based on genotypic/histotypic strata mentioned in Section 5.1 (Inclusion Criteria). Specific mutations are also defined in Appendix 9. Eligible mutations will be based on prior genotyping results using a clinically validated or qualified test. This test may have been performed on either tumor tissue or ctDNA samples. Sites must provide the Sponsor with the report. Archival tumor tissue will be collected for central laboratory testing. Details on processes for collection and shipment can be found in the laboratory manual. Fresh pretreatment biopsies will be mandatory for subjects who do not have available archival specimen tissue preferably from within 3 years, unless the investigator determines that the tumor site is not amenable to biopsy or poses a significant risk to the subject's safety. Subjects who neither have archival tumor tissue samples nor can provide fresh pretreatment biopsies may still be eligible to participate in the study with agreement from the Sponsor Medical Monitor. The Sponsor will evaluate this requirement on a case-by-case basis. In the event of a discrepancy between the local and central testing results for the eligibility defining mutation, the subject will remain on study. For data analysis purposes, results from the central laboratory will supersede those of the local laboratory.

Information regarding genetic research is provided in Appendix 5.

8.8. Other Biomarkers

Archival tumor samples will be collected for all subjects. These samples will be used to confirm mutations identified on the genomic report provided at enrollment. Archival samples will also be used to assess and evaluate potential markers of response to RMC-4630 and sotorasib combination therapy, including but not limited to deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein expression. If tumor tissue allows, the remaining archival tumor samples may be stored for future development of companion diagnostic.

Blood samples will be drawn as outlined in the SoA (Table 1) and Table 2 from every subject in order to extract and analyze ctDNA to assess and evaluate potential peripheral biomarkers of response to sotorasib and RMC-4630. Samples may be analyzed retrospectively.

Note, biomarker sample collection applies to the main protocol only and not the Extended-Use phase.

9. STATISTICAL CONSIDERATIONS

This is a Phase 2 multicenter, open-label study evaluating the efficacy, safety, tolerability, and PK of RMC-4630 in combination with sotorasib in subjects with *KRAS*^{G12C} mutant locally advanced or metastatic NSCLC after failure of prior standard therapy. Descriptive statistics will be used to summarize baseline demographic and disease characteristics, treatment administration, efficacy, and safety outcomes, and PK parameters.

Descriptive summaries of discrete data will present the number of study subjects and the incidence as a frequency and as a percentage. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size.

A final analysis will be performed at the EOS as defined in Section 4.4.

9.1. Statistical Hypotheses

No formal statistical hypothesis will be tested.

9.2. Sample Size Determination

Up to a total of [redacted] cts will be enrolled into this study. Approximately [redacted] jects will be enrolled during the safety run-in portion of the study. Initially, up to [redacted] will be enrolled and treated at the dose of [redacted] of each week in a 21-day cycle in combination with sotorasib at 960 mg QD. An additional [redacted] may be enrolled to receive RMC-4630 [redacted] of each week in a 21-day cycle in combination with sotorasib at 960 mg QD, if a decision is made to increase the RMC-4630 dose from [redacted] mg. After completion of the safety run-in (DLT clearance) of both dose levels, additional subjects may be enrolled for the purpose of dose optimization to inform the selection of the final expansion dose. Expansion may commence as soon as the final expansion dose has been selected. Approximately [redacted] will be enrolled for dose optimization and dose expansion.

With a total sample size of [redacted], the probability of observing at least 1 AE with an incidence rate of 5% is at least 90%.

The ORR will be reported by dose level pooling subjects from safety run-in and dose optimization (if applicable) and expansion. It's anticipated that approximately [redacted] ects will be treated at the final expansion dose depending on the actual number of subjects enrolled during safety run-in and/or dose optimization. For the final expansion dose, with [redacted] the lower bound of the one-sided 80% exact CI will be above 33.7% and 37.3% respectively if the observed response rate is 45%.

The mutational status of each subject and, thus, placement into Cohort 1 or 2 (see Section 4.1) will be determined based on the historic genomic reports and later might be adjusted based on ctDNA analysis results collected at baseline. Therefore, the sample size for one or both cohorts will depend on the distribution of mutational status.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined in Table 8.

Table 8: Population Definitions

Population	Description
Treated	All subjects who take at least 1 dose of study treatment
Evaluable	**DLT-evaluable**: All subjects in the safety population who have received at least 80% of planned dose of sotorasib and at least 4 of 6 doses of RMC-4630 in Cycle 1 and have been observed for safety assessments for the full 21 days of the DLT evaluation period. Subjects who experience a DLT within the DLT period will be considered DLT evaluable regardless of the amount of study treatment received or completion of the observation period. **Evaluable for efficacy**: All subjects with measurable disease at baseline, who take at least 1 dose of study treatment and (1) undergo 1 post-baseline response assessment or (2) who die or (3) had clinical progression prior to the first post-baseline response assessment.

Abbreviations: DLT = dose-limiting toxicity.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the planned statistical analyses.

Unless otherwise specified, efficacy analyses will be based on the efficacy-evaluable population and will be summarized by the initial combination dose level. Efficacy analyses will be presented for Cohort 1 and Cohort 2 separately, and for the overall study population.

The primary efficacy endpoint is ORR, defined as the proportion of subjects who achieve a CR or PR per RECIST v1.1. The estimated proportion and the corresponding 95% two-sided exact CI using the Clopper-Pearson method will be derived for ORR.

Secondary efficacy endpoints and analyses include the following:

- DCR is defined as the proportion of subjects who achieve a CR or PR or SD per RECIST v1.1. DCR will be analyzed similarly as ORR.
- DOR is defined as the interval from the first documentation of CR or PR to first documentation of definitive disease progression or death due to any cause, whichever occurs first. Subjects who are still alive and free from progression at the time of the data cutoff date, are lost to follow-up, have discontinued from the study, or have initiated subsequent anticancer therapy will be censored at the last adequate tumor assessment. Subjects who never achieve a response (PR or better) will be excluded from the analysis of DOR.
- PFS is defined as the interval from the first dose of study treatment to documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. Subjects who are still alive and free from progression at the time of the data cutoff date, are lost to follow-up, have discontinued from the study, or who have initiated subsequent anticancer therapy will be censored at the last adequate tumor assessment. PFS will be summarized for the all-treated population.

- Overall survival (OS) is defined as the interval from the first dose of study treatment to death due to any cause. Subjects who are not known to have died will be censored at the last known alive date. OS will be summarized on the all-treated population.

The Kaplan-Meier method will be used to estimate DOR, PFS and OS curves and corresponding quartiles. The Kaplan-Meier median will be calculated with a two-sided 95% CI.

9.4.2. Safety Analyses

All DLT assessments will be performed on the DLT-evaluable population (see Section 8.4 for DLT assessment details). All other safety analyses will be performed on the Treated Population. Safety analyses will be descriptive in nature, and will include analyses of DLTs, AEs, SAEs, AEs leading to study treatment discontinuation and/or dose modification, clinical laboratory tests, vital signs, and ECGs. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Unless otherwise specified, AEs will be summarized by primary MedDRA system organ classes and Preferred Term. Safety analyses will be summarized by the initial combination dose level. Safety analyses will be presented for each cohort separately and for the overall study population.

During dose expansion after the final expansion dose has been selected, evaluation of all Grade 4 or higher treatment-related adverse event rates will be conducted to assess if the unacceptable toxicity threshold has been reached. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data. After reviewing the totality of data from both CodeBreaK 101C and cumulative data from this study, one of the following actions may be taken:

1. Terminate the study
2. Amend the protocol to potentially improve the benefit/risk for subjects (eg, increase safety monitoring, modify dose/schedule, mandate premedication)
3. Continue dose expansion without any changes

The stopping rules use a Bayesian approach to pause the enrollment if the posterior probability is ≥ 80% that the Grade 4 or higher treatment-related adverse event rate is greater than 20%. The stopping boundaries shown in Table 9 assume a prior distribution of Beta (0.4, 1.6). The operating characteristics with the pre-specified batch size of 10 new subjects are summarized in Table 10.

Table 9: Stopping Boundary by Number of Subjects

Number of Subjects Treated	Number of Subjects with Grade 4 or Higher Treatment-Related Adverse Events to Halt Enrollment
10	≥ 4
20	≥ 6
30	≥ 9
40	Expansion complete

Table 10: Operating Characteristics of Stopping Rules

True Grade 4 or Higher Treatment-Related Adverse Event Rate	Probability of Early Stopping of Dose Expansion	Average Dose Expansion Sample Size
0.1	2.1%	39
0.15	9.7%	38
0.2	25.8%	34
0.25	47.7%	29
0.3	69.2%	23

9.4.3. Pharmacokinetic Analyses

Concentrations of RMC-4630 and sotorasib will be summarized descriptively by timepoint. Concentrations of RMC-4630 may be used for population PK analysis and presented in a separate report.

9.4.4. Other Analyses

Additional efficacy and biomarker exploratory analyses will be described in the Statistical Analysis Plan (SAP) finalized before database lock.

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APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

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 (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), current RMC-4630 Investigator's Brochure (IB), and other relevant documents (eg, subject information, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Financial Disclosure

Investigators and sub investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after study completion.

Informed Consent Process

- The investigator or his/her designated representative will explain the nature of the study to the subject and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Per IRB/IEC requirements, subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject.

Subjects who are re-screened are not required to be re-consented; all re-screening should occur within 5 days of the initial date of the screen failure (see Section 5.4)

The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Any remaining mandatory samples may be used for optional exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

- The posting of company Sponsored clinical trial information and tabular study results on the United States (US) National Institute of Health (NIH) website (www.clinicaltrials.gov) and on other regional clinical trial registries in countries or regions where the clinical trial is conducted, will comply with local regulations.
- Periodic safety reports will be submitted as required by regulation in the countries where the study is conducted.

Data Quality Assurance

- All subject data relating to the study will be recorded on electronic Case Report Form (eCRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the Case Report Form (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/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the 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 (eg, contract research organizations [CROs]).
- Study monitors will perform ongoing source data verification 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 subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a period of 2 years following the date a marketing application is approved for RMC-4630 for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved fur such indication, until 2 years after the investigation is discontinued and US Food and Drug Administration (FDA) is notified (ie, in accordance with 21 CFR 312.62(c), 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.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the collected data. Source documents are filed at the investigator's site.
- Data entered on the CRF or entered in the 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.

Study and Site Closures

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

The investigator may initiate study site closure at any time, 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:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

Publication Policy

- The Sponsor will comply with the requirements for publication of study results, and the results of this study may be published or presented at scientific meetings. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement. The coordinating 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.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS AND REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

- The tests detailed in Table A2-1 will be performed by the local laboratory.
- Protocol specific- requirements for inclusion or exclusion of subjects are detailed in Section 5.1 and Section 5.2 of the protocol, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing: Refer to Section 5.1 for screening criteria, to Appendix 4 for women of childbearing potential (WOCBP) criteria, and to the Schedule of Activities (SoA; Table 1) for timepoints.
- The results of each test must be entered into the electronic Case Report Form (eCRF).
- Investigators must document their review of each laboratory safety report.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	RBC Count	RBC Indices: MCV, MCH, % Reticulocytes		
	Hemoglobin	WBC count with Differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Bands (if available)		
	Hematocrit			
	Platelet count			
Clinical Chemistry [1]	Sodium	Potassium	Chloride	Bicarbonate/Carbon Dioxide
	Blood urea nitrogen	Creatinine	Glucose (non-fasting)	Total Protein
	Albumin	Phosphorus	Calcium	Magnesium
	Uric Acid	ALT/AST	Total and direct bilirubin	ALP
	Gamma-glutamyl transferase	Lipase		
CPK isoenzymes [2]	Total and skeletal muscle (MM) component (not required for screening purposes)			
Coagulation Tests	Prothrombin time/INR, aPTT or PTT			
Routine Urinalysis	Appearance, specific gravity, pH, glucose, protein/albumin, blood, ketones, bilirubin, urobilinogen, nitrites, leukocyte esterase Microscopic examination (if blood or protein is abnormal)			

Table A2-1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Other Screening Tests	Follicle stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) [3] Highly sensitive blood or urine hCG pregnancy test (as needed for women of childbearing potential) [4] Serology [5]: HBsAg, HBcAb, and hepatitis C virus antibody. Additional testing (eg, hepatitis B viral load, HBsAb, hepatitis B core IgM antibody) may be required if results are inconclusive or positive for surface antigen/core antibody.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CPK = creatine phosphokinase; hCG = human chorionic gonadotropin; HBcAb = hepatitis B virus core antibody; HBsAg, hepatitis B virus surface antigen; IEC = Independent Ethics Committee; IRB, Institutional Review Board; INR, international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PTT = partial thromboplastin time; RBC = red blood cell; SAE = serious adverse event; ULN = upper limit of normal; WBC = white blood cell.

[1] Concurrent elevation of AST or ALT >3 × ULN AND total bilirubin >2 × ULN or INR >1.5 in the absence of cholestasis and other causes (eg, viral hepatitis, other pre-existing or acute liver disease, or another drug capable of the observed injury), which may indicate severe drug-induced liver injury (possible Hy's law case). All events with the defined biochemical abnormalities must be reported as an SAE; and study medications should be permanently discontinued.

[2] Variations of CPK isoenzymes are acceptable (CK, CKMB, Troponin I)

[3] See Appendix 4.

[4] Local urine testing will be standard for the protocol unless blood testing is required by local regulation or IRB/IEC. For screening, a blood test is required.

[5] For Serology:

- Negative HBsAg test is required at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening. (The HBV DNA test must be performed for subjects who have a negative HBsAg test and a positive total HBcAb test.)
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening.

Review and Assessment of Potential Hy's Law Cases

The investigator is responsible for determining whether a subject meets potential Hy's Law criteria at any point during the study. All sources of hepatic biochemistry laboratory data available to the investigator should be reviewed to identify potential Hy's Law events; this includes samples taken at scheduled study visits and other visits, including central and all local laboratory evaluations, even if collected outside of the study visits.

The following are the key components used to detect potential Hy's Law cases:

- Hepatocellular injury, indicated by 3-fold or greater elevations above the upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
- Elevation of serum total bilirubin to >2 × ULN (suggesting hepatic functional compromise), without initial findings of cholestasis (elevated serum alkaline phosphatase [ALP])
- No other reason can be found to explain the combination of increased aminotransferase(s) and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Any potential Hy's Law case (as described above) should be handled as a serious adverse event (see reporting requirements in Appendix 3) associated with the use of the drug and reported to the Sponsor promptly (ie, even before all other possible causes of liver injury have been

excluded). It should be promptly reported to the Sponsor before fully working up the subject to rule out other etiologies. The case should be reported with the seriousness criterion of medically significant selected, and should include all available information, especially that needed for evaluating the severity and likelihood that the drug caused the reaction and should initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

APPENDIX 3. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of Adverse Event (AE)

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease or laboratory value changes that require treatment or adjustment to current study therapy). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term 'life threatening' in the definition of 'serious' refers to an event in which the subject 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 had been more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject 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 (AEs). If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
f. Other situations • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject 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 other 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. Potential Hy's Law cases that meet the description outlined in Appendix 2 should be reported as SAE.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an adverse event (AE)/serious adverse event (SAE) occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event and report pertinent information.
- The investigator will then record all relevant AE/SAE information in the electronic case report form (eCRF). Additionally, investigative sites should report SAEs within 24 hours of becoming aware of the event using the paper SAE report form. See section below on the reporting of SAEs.
- It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the AE/SAE Case Report Form (CRF) and SAE report form. Only pertinent information should be reported.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all subject identifiers, with the exception that the subject number will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity (severity) for each AE and SAE reported during the study using the definitions found in the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5 (NCI CTCAE v5) or later. The NCI CTCAE v5 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. If a subject experiences any AE not listed in the NCI CTCAE v5, the following grading system should be used to assess severity:

- Grade 1 (Mild) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate) – experiences which introduce some level of inconvenience or concern to the subject, and that may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe) – experiences that are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life threatening) – experiences that cause the subject to be in danger of life-threatening consequences and urgent intervention is required
- Grade 5 (Death) – experiences which result in subject death

The terms "severe" and "serious" are not synonymous. An AE that is assessed as Grade 3 or 4 should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3 or 4. An event is defined as serious when it meets at least 1 of the predefined seriousness, as described in the definition of an SAE, **not** only when it is rated as Grade 3 or 4.

Assessment of Causality

- The investigator is obligated to assess the relationship between both study interventions/study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and applicable prescribing information in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data within 24 hours of receipt of the information on an updated SAE report form to either the email or fax listed below.

Reporting of SAES

SAE Reporting to the Sponsor or Designee via Paper CRF

- Investigative sites should report SAEs within 24 hours of becoming aware of the event to the Fortrea Pharmacovigilance department using the paper SAE report form and any supporting documentation either by email or fax.

  Email: SAEIntake@fortrea.com

  Fax: 1 888 887 8097
- In rare circumstances and in the absence of email or facsimile equipment, notification by telephone to the Medical Monitor is acceptable with a copy of the SAE report form sent to Fortrea when email and fax becomes available.
- Contacts for SAE reporting and the SAE report form can be found in the Regulatory binder.

APPENDIX 4. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions

Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

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

   Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

   A high follicle stimulating hormone (FSH) and estradiol level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH and estradiol measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

CONTRACEPTIVES[1] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[2] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen only hormone contraception associated with inhibition of ovulation [3]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[3]
• Bilateral tubal occlusion
Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods [3] That Are User Dependent Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [3] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation [3] • oral • injectable
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are NOT acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

[1] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. Contraceptive requirements do not apply to subjects who are exclusively in same sex relationships.

[2] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[3] Hormonal contraception efficacy may potentially be decreased due to interaction with sotorasib thus male condoms must be used in addition to hormonal contraception.

COLLECTION OF PREGNANCY INFORMATION

Male Subjects with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This

applies only to male subjects who receive RMC4630 and sotorasib under this protocol.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form provided in the regulatory binder and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects Who Become Pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (SAE), any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor pregnancy information on the appropriate form provided in the regulatory binder. While the investigator is not obligated to actively seek this information in former study subjects, he/she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study treatment and be withdrawn from the study.

APPENDIX 5. GENETICS

Use and Analysis of Tumor DNA during the Main Protocol

- Genetic variation in tumor tissue may impact a subject's response to study treatment, 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) allow, blood and tumor tissue samples will be collected for DNA analysis from consenting subjects.
- DNA samples from tumor tissue will be retrospectively analyzed to explore clinical activity in subjects with specific molecular abnormalities. In addition, predefined biomarkers for the sensitivity to *SHP2* and/or *MEK1/2,* and *EGFR* will be evaluated.
- DNA extracted from archival subject tumor tissue will be used to evaluate if a subject has specific tissue abnormalities in their DNA that may be sensitive to our RMC4630 and sotorasib. This information will be used to confirm if a subject has the same mutations as their local genetic results (noncentralized testing laboratory) report. The local report is the basis for eligibility assessment.
- Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- DNA and RNA from blood and archival tumor tissue will be used for research related to study treatment or non-small cell lung cancer (NSCLC) and/or other solid tumors. Genetic research will include biomarkers of sensitivity in blood, including but not limited to circulating tumor deoxyribonucleic acid (ctDNA). Whole exome and transcriptome studies, which will be conducted on archival tissue (or fresh if archival is not available) to explore if DNA and RNA can help identify potential biomarkers associated with response to RMC-4630 and sotorasib.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.

The Sponsor will remove all subject identifiers from the subject samples to inhibit recognition or reidentification. The anonymized DNA samples will be stored in a secure storage space prior to testing for markers of drug sensitivity. All samples will be processed and analyzed for the purposes of this study and the output will be anonymized subject data, which may be applied for future research.

Subject sample retention will not exceed 10 years after the final study results have been reported as per local requirements.

APPENDIX 6. RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS (RECIST V1.1)

For this study, response and progression will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumours guideline version 1.1 (RECIST v1.1; Eisenhauer,2009).

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows.

a. Measurable 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 of:

- 10 mm by computed tomography (CT) or magnetic resonance imagining (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20 mm by chest X-ray

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

b. Nonmeasurable Tumor Lesions

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

c. Special Considerations Regarding Lesion Measurability

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

Bone Lesions:

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

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

- Blastic bone lesions are nonmeasurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor nonmeasurable) since 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 noncystic lesions are present in the same subject, 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. Study protocols should detail the conditions under which such lesions would be considered measurable.

Specifications by Methods of Measurements

Measurement of Lesions

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

Methods of Assessment

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

a. Clinical Lesions

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

b. Chest X-Ray

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

c. CT and MRI

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

d. Ultrasound

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

e. Endoscopy and Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

f. Tumor Markers

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response.

g. Cytology and Histology

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

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

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

Baseline Documentation of "Target" and "Nontarget" Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 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 if a subject has only one or 2 organ sites involved, a maximum of 2 and 4 lesions, respectively, will be recorded.

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

Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 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 but <15 mm) should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

Sum of Diameters

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

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

Response Criteria

a. Evaluation of Target Lesions

Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm).
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

Response	Evaluation of Target Lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. NOTE: the appearance of one or more new lesions is also considered progression.

b. Special Notes on Assessment of Target Lesions

Lymph Nodes:

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

Target Lesions that Become "Too Small to Measure":

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as "too small to measure."

When this occurs, it is important that a value be recorded on the case report form. 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, but too small to measure, a default value of 5 mm should be assigned (derived from 5-mm slice thickness).

Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly, but too small to measure, a default value of 5 mm should be assigned in this circumstance as well. To reiterate, however, if the radiologist is able to provide an actual measurement, it should be recorded even if it is below 5 mm.

Lesions that Split or Coalesce on Treatment:

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

c. Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. Although some nontarget lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

Response	Evaluation of Nontarget Lesions
Complete Response (CR)	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis)
Non-CR/ Non-PD	Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal existing nontarget

d. Special Notes on Assessment of Progression of Nontarget Disease

When the Subject Also Has Measurable Disease

In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to quality for unequivocal progression status. The face of SD or PR of target disease will therefore be extremely rare.

When the Subject Has Only Nonmeasurable Disease

This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in "volume," which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. 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 (ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor [eg, some "new" bone

lesions that may be simply healing or flare of pre-existing lesions]). This is particularly important when the subject's baseline lesions show partial or complete response. 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 on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

f. FDG-PET

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion
  - A positive FDG-PET scan lesion is one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD. A "positive" FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The subject's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions.

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table A6-1 provides a summary of the overall response status calculation at each timepoint for subjects who have measurable disease at baseline.

When subjects have nonmeasurable (therefore nontarget) disease only, Table A6-2 is to be used.

Table A6-1 Timepoint Response: Subjects with Target Lesions (with or without Nontarget Lesions)

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

Abbreviations: CR = complete response; NE, = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table A6-2 Time Point Response: Subjects with Nontarget Lesions Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease.

[1] "Non CR/non PD" is preferred over "stable disease" for nontarget disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Unevaluable Designation

When no imaging/measurement is done at a specific time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and, during the study, only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

c. Best Overall Response: All Timepoints

The best overall response is determined after all data for the subject is known.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point, as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table A6-3.

Table A6-3 Best Overall Response when Confirmation Is Required

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[1] If a CR is truly met at the first timepoint, any disease n at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

d. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be

based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the CRF.

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a subject with timepoint responses of PR-NE-PR as a confirmed response.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and nontarget disease as shown in Table A6-1.

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

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

For equivocal findings of progression (eg, 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.

APPENDIX 7. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

ECOG Performance Status

0	Fully Active, Able to Carry on All Pre-Disease Performance Without Restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Abbreviations: ECOG = Eastern Cooperative Oncology Group.

APPENDIX 8. LIST OF PROHIBITED MEDICATIONS WHILE RECEIVING TREATMENT

A partial list of drug classes that potentially prolong corrected QT segment (QTc), are strong Cytochrome-P450 (CYP)3A inhibitors and/or inducers, are CYP3A sensitive substrates, or are P-Glycoprotein (P-gp) sensitive substrates is provided below.

Medications known to prolong QTc		
Amiodarone	Anagrelide	Arsenic Trioxide
Azithromycin	Chloroquine	Chlorpromazine
Cilostazol	Ciprofloxacin	Citalopram
Disopyramide	Dofetilide	Donepezil
Dronedarone	Droperidol	Erythromycin
Escitalopram	Flecainide	Fluconazole
Haloperidol	Ibutilide	Levofloxacin
Methadone	Moxifloxacin	Ondansetron
Oxaliplatin	Pentamidine	Pimozide
Procainamide	Propofol	Quinidine
Sevoflurane	Sotalol	Thioridazine
Vandetanib		
Proton Pump Inhibitors (PPIs)		
Omeprazole	Lansoprazole	Dexlansoprazole
Rabeprazole	Pantoprazole	Esomeprazole
H-2 Receptor Antagonists		
Ranitidine	Famotidine	Cimetidine
Nizatidine		
Strong CYP3A Inhibitors		
Boceprevir	Itraconazole	Ritonavir
Clarithromycin	Ketoconazole	Saquinavir and ritonavir
Cobicistat	Lopinavir and ritonavir	Telaprevir
Danoprevir and ritonavir	Nefazodone	Tipranavir and ritonavir
Elvitegravir and ritonavir	Nelfinavir	Telithromycin
Grapefruit juice	Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)	Troleandomycin
Idelalisib	Posaconazole	Voriconazole
Indinavir and ritonavir		

Strong CYP3A Inducers		
Apalutamide	Mitotane	St. John's wort
Carbamazepine	Phenytoin	Enzalutamide
Rifampin		
Sensitive CYP3A4 Substrates (require Principal Investigators' review and approval)		
Alfentanil	Avanafil	Buspirone
Conivaptan	Darifenacin	Darunavir
Ebastine	Everolimus	Ibrutinib
Lomitapide	Lovastatin	Midazolam
Naloxegol	Nisoldipine	Saquinavir
Simvastatin	Sirolimus	Tacrolimus
Tipranavir	Triazolam	Vardenafil
Budesonide	Dasatinib	Dronedarone
Eletriptan	Eplerenone	Felodipine
Indinavir	Lurasidone	Maraviroc
Quetiapine	Sildenafil	Ticagrelor
Tolvaptan		
Strong P-gp Inhibitors		
Amiodarone	Carvedilol	Clarithromycin
Dronedarone	Itraconazole	Lapatinib
Lopinavir and Ritonavir	Propafenone	Quinidine
Ranolazine	Ritonavir	Saquinavir and Ritonavir
Telaprevir	Tipranavir and Ritonavir	Verapamil
Sensitive P-gp Substrates (require Principal Investigators' review and approval)		
Dabigatran Etexilate	Digoxin	Fexofenadine

Please note that this list is not comprehensive.
The list and updates of medications that are known to prolong QTc may be obtained from www.crediblemeds.org.
Additional information and updates concerning strong CYP3A inhibitors and inducers, and strong P-gp inhibitors can be found at www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractions Labeling/ ucm093664.htm.
In addition, consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. Contact the Medical Monitor if questions arise regarding medications not listed.

APPENDIX 9. POTENTIAL GENETIC MODIFIERS FOR ENROLLMENT INTO DOSE EXPANSION

The listed genotypic mutations will be used to categorized subjects, based on their genomic report. The Sponsor may be contacted to assist in the identification of mutations that may not be listed in this appendix.

Cohort 1 – only *KRAS*^{G12C} NSCLC (without any potential genetic modifiers)

Cohort 2 – including the following:

- STK11/LKB1
- KEAP1
- PIK3CA
- BRAF Class 1/2/unclassified
- ATRX
- BRCA2

APPENDIX 10. CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, pandemic, natural disaster, or terrorist attack) may prevent access to the clinical trial site.

For an emergency that prevents access to the study site, possible contingency measures are suggested below in order to ensure the safety of subjects, consider continuity of clinical study conduct, protect trial integrity, and assist in maintaining compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP).

Procedure modifications that may be considered in the event of a regional or national emergency declared by a governmental agency include the following:

- If onsite visits are not possible, remote visits may be considered for the collection of possible data.
- If onsite visits are not possible, noncritical assessments could be omitted.
- Visit windows may be extended in cases where required assessments cannot be
- obtained remotely.
- Use of local laboratory locations may be allowed.
- The direct-to-patient (DTP) supply of study medication from the PI/site/Sponsor may be allowed by local regulations and agreed upon by the subject.

Contingencies implemented due to emergency will be documented.

For the duration of the emergency, Sponsor agreement must be obtained prior to the implementation of these procedure modifications.

It is the investigator's responsibility to protect the rights, safety, and well-being of study subjects. Investigators must be able to manage and oversee study conduct and the safety of study subjects in order to continue enrolling and treating subjects in the study. During the emergency, if the site is unable to adequately follow protocol-mandated procedures, screening and administration of study treatment may be temporarily delayed.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The subject or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension or use of local laboratories).

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized in the clinical study report (eg, study discontinuation or discontinuation/delay/omission of the study treatment due to the emergency). Any additional analyses and methods required to evaluate the objectives and endpoints of the study (eg, missing data due to the emergency) will be detailed in the statistical analysis plan.

APPENDIX 11. MODIFIED TOXICITY PROBABILITY INTERVAL-2 (MTPI-2) DESIGN DETAILS

Dose escalation/de-escalation during the safety run-in phase will follow an mTPI-2 algorithm (Guo, 2017), with a target dose-limiting toxicity (DLT) probability of 0.30 and the acceptable toxicity probability interval of 0.25 to 0.35.

DLT assessment will be performed on the DLT-evaluable population (see Section 9.3), as guided by the following mTPI-2 decision table.

Dose Escalation Rule of the Modified Toxicity Probability Interval-2 Method								
		Number of DLT–Evaluable Subjects Treated at Current Dose						
		3	**4**	**5**	**6**	**7**	**8**	**9**
Number of Dose-Limiting Toxicities	**0**	E	E	E	E	E	E	E
	1	S	S	E	E	E	E	E
	2	D	D	D	S	S	S	E
	3	DU	DU	D	D	D	D	S
	4		DU	DU	DU	D	D	D
	5			DU	DU	DU	DU	DU
	6				DU	DU	DU	DU
	7					DU	DU	DU
	8						DU	DU
	9							DU

Source: Guo W, Wang SJ, Yang S, et al. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. *Contemp Clin Trials*. 2017;58:23-33.
Abbreviations: D = de-escalate to the next-lower dose; DLT = dose-limiting toxicity; DU = de-escalate to the next-lower dose and the current dose will never be used again because of unacceptable high toxicity (ie, the probability that the DLT rate is higher than 30% at the current dose is greater than 95%); E = escalate to the next-higher dose; S = stay at the current dose.

APPENDIX 12. ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATE	arterial thromboembolic events
BCVA	best corrected visual acuity
BIW	twice weekly
BRAF Class 3	class 3 type mutations in *BRAF*
BRAT	banana, rice, apples, toast
BUN	blood urea nitrogen
C1, Cx, etc	Cycle 1, Cycle x, etc
C1D1, CxDx, etc	Cycle 1 Day 1, Cycle x Day x, etc
CAP	College of American Pathologists
CBC	complete blood count
CDX	cell-line-derived xenograft
CFR	Code of Federal Regulation
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRISPR	clustered regularly interspaced short palindromic repeats
CRO	contract research organization

Abbreviation	Definition
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CYP	cytochrome P-450
D1, Dx, etc	Day 1, Day x, etc
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DTP	direct-to-patient
EC_{50}	50% effective concentration
EC_{75}	75% effective concentration
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOS	End of Study
EOT	End-of-Treatment
ERK	extracellular signal-regulated kinase
FFPE	formalin fixed; paraffin embedded
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GAP	GTPase activating protein
GCP	Good Clinical practice
GDP	guanosine diphosphate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GTP	guanosine triphosphate

Abbreviation	Definition
H2-blockers	H2-receptor antagonists
HA	Health Authorities
HCV	hepatitis C virus
HDPE	high-density polyethylene
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
ILD	interstitial lung disease
INR	international normalized ratio
IRB	Institutional Review Board
ISMC	Internal Safety Monitoring Committee
IUD	Intrauterine device
IUS	intrauterine hormone-releasing system
KRAS	*Kirsten rat sarcoma viral oncogene homolog*
$KRAS^{G12C}$	*KRAS with a mutation at codon 12*, which encodes glycine (G) to cysteine (C)
LLN	lower limit of normal
LMWH	low molecular weight heparin
LSLV	last subject, last visit
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval-2
MUGA	multigated acquisition

Abbreviation	Definition
NCI CTCAE v5	National Cancer Institute Common Terminology Criteria for Adverse Events Version 5
NF1	*neurofibromin 1*
$NF1^{LOF}$	mutations in *NF1* predicted to result in loss of function
NIH	National Institute of Health
NRAS	*neuroblastoma RAS viral oncogene homolog*
NSCLC	non–small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PDAC	pancreatic ductal adenocarcinoma
PDGF-R	platelet-derived growth factor receptor
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-Glycoprotein
PIC	powder-in-capsule
PK	pharmacokinetic(s)
PO	oral(ly)
PPI	proton pump inhibitors
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumours, Version 1.1
RNA	ribonucleic acid

Abbreviation	Definition
ROS1	reactive oxygen species proto-oncogene 1
RP2D/RP2DS	recommended Phase 2 dose/recommended Phase 2 dose and schedule
RPED	retinal pigment epithelial detachment
RTK	receptor tyrosine kinase
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SHP2	Src homology 2 domain-containing protein tyrosine phosphatase 2
SJS	Stevens-Johnson syndrome
SoA	Schedule of Activities
SOC	standard-of-care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
TEN	toxic epidermal necrolysis
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
VEGF-R	vascular endothelial growth factor receptor
VTE	venous thromboembolic events
WBC	white blood cell
WOCBP	women of childbearing potential