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NCT #: NCT04119453

STATISTICAL ANALYSIS PLAN (SAP)

A Phase 2 Open-Label, Multicenter, Study to Evaluate the Efficacy and Safety of Rivoceranib in Subjects with Recurrent or Metastatic Adenoid Cystic Carcinoma of All Anatomic Sites of Origin

Protocol Number:	RM-202
Investigational Product	Rivoceranib
Development Phase:	2
Sponsor:	Elevar Therapeutics, Inc. 2825 E Cottonwood Pkwy, Suite 180 Salt Lake City, UT 84121 USA
Protocol Amendment:	Amendment 4
Protocol Date:	22 October 2020
SAP Version:	V2.0
SAP Date:	18 February 2022

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Protocol Number:	RM-202
Protocol Amendment:	Amendment 4 (22 October 2020)
SAP Version:	2.0

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Version History

Version and Date	Description
Version 1.0, 17 March 2021	Initial version
Version 2.0, 18 February 2022	Second version

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List of Abbreviations and Definitions of Terms

ABBREVIATION	DEFINITION
ADI	Actual dose intensity
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BICR	Blinded Independent Central Review
BMI	Body mass index
BOR	Best overall response
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
FACT-G	Functional Assessment of Cancer Therapy - General
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
PN	Preferred name
RECIST	Response Evaluation Criteria in Solid Tumors v1.1
SAE	Serious adverse advent
SAP	Statistical Analysis Plan
SD	Stable disease
SMQ	Standardized MedDRA query
SOA	Schedule of assessments
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TTP	Time to progression
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methodology and analyses to be conducted for Elevar Therapeutics protocol RM-202 (Amendment 4; 22 October 2020). Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report.

2 STUDY OBJECTIVES AND ENDPOINTS

The primary objectives and endpoints for the study are as follows.

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Table 1: Study Objectives and Endpoints

Objectives and Endpoints	**Primary Objectives:**	**Primary Endpoints:**
	To evaluate the efficacy of rivoceranib in subjects with recurrent or metastatic ACC based on assessment of objective response rate (ORR).	• ORR per the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 by Investigator or Institutional assessment. • ORR per the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 evaluated by Blinded Independent Central Review
	Secondary Objectives:	**Secondary Endpoints:**
	To further evaluate the efficacy in subjects with recurrent or metastatic ACC: • Overall survival (OS) • Progression free survival (PFS) • Duration of Response (DOR) • Time to progression (TTP) • To evaluate Disease control rate (DCR) based on RECIST v1.1	Efficacy assessed by: • OS at 1 year and 2 years • PFS at 6 months, 12 months and 2 years per RECIST v1.1 by Investigator or Institutional assessment • PFS at 6 months, 12 months and 2 years per RECIST v1.1 evaluated by Blinded Independent Central Review (BICR) • DOR per RECIST v1.1 by Investigator or Institutional assessment • DOR per RECIST v1.1 evaluated by Blinded Independent Central Review • TTP per RECIST v1.1 by Investigator or Institutional assessment • TTP per RECIST v1.1 evaluated by Blinded Independent Central Review • DCR per RECIST v1.1 by Investigator or Institutional assessment • DCR per RECIST v1.1 by Blinded Independent Central Review

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	To evaluate the safety of rivoceranib	Safety assessments (e.g., new adverse events (AEs), AEs present at baseline that worsen in severity during the study, and clinical laboratory abnormalities)
	Exploratory Objectives:	**Exploratory Endpoints:**
	To further evaluate the efficacy in subjects with recurrent or metastatic ACC based on the CHOI criteria: • ORR • PFS • DOR • TTP • DCR	Efficacy assessed by: • ORR per CHOI criteria evaluated by Blinded Independent Central Review. (freehand measurement of tumor is preferred but circular is permitted) • PFS at 6 months, 12 months and 2 years per CHOI criteria evaluated by Blinded Independent Central Review • DOR per CHOI criteria evaluated by Blinded Independent Central Review • TTP per CHOI criteria evaluated by Blinded Independent Central Review • DCR per CHOI criteria evaluated by Blinded Independent Central Review
	To explore pharmacodynamic markers	Correlate presence of *MYB* or *MYB-L1* translocations with response to rivoceranib
	To evaluate the pharmacokinetics (PK) of rivoceranib	PK parameters including: • Maximum observed serum concentration (C_{max}) • Time of peak concentration (T_{max}) • Area under the serum concentration-time curve (AUC) • Clearance (CL/F) • Terminal elimination half-life ($t_{1/2}$)
	To evaluate quality of life measurements during treatment with rivoceranib	Global Health Status/Quality of Life score according to Functional Assessment of Cancer Therapy (FACT)-G

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3 STUDY OVERVIEW

3.1 Study Design

This is a Phase 2, multicenter, open-label study designed to evaluate the efficacy and safety of rivoceranib in subjects with recurrent or metastatic ACC of all anatomic sites of origin. Approximately 72 subjects will be enrolled at approximately 12 sites.

After informed consent and screening procedures have been performed, eligible subjects will receive a starting dose of 700 mg rivoceranib every day continuously during 28-day cycles. To ensure safety of subjects, the dose of rivoceranib may be reduced when the toxicities are judged by the Investigator to be at least possibly related to rivoceranib treatment.

The actual dose received and the start and stop of dosing will be captured on the electronic case report form (eCRF) and will be used to calculate dose administered and duration of treatment.

Subjects will be evaluated at regular clinic visits approximately every 2 weeks for safety assessments. After completion of cycle 3, subjects will be followed up every 2 weeks or every 4 weeks based on Investigator's judgment. On Day 1 of each cycle, a physical examination will be conducted and AEs, current medications, laboratory tests, vital signs and ECOG performance status will be evaluated. Periodic single 12-lead electrocardiograms (ECGs) will be obtained.

Tumor response and progression will be assessed by a local imaging facility 8 weeks after initiation of rivoceranib during the first year and at every 12 weeks thereafter until End of Treatment (EOT). Subject treatment decisions will be made based on local imaging results and Investigator evaluation which will be entered into the eCRFs. Local imaging results will determine the subject's tumor response and date of progression according to RECIST v1.1. All scans should be available for submission to central archiving and Blinded Independent Central Review.

For subjects who have stable disease (SD) or better and are tolerating therapy well, treatment with rivoceranib may continue until disease progression, intolerable side effects occur, death or the subject withdraws consent from the treatment.

After treatment is discontinued for any reason, an EOT visit will be conducted to gather safety data for the subject within 7 days (± 7 days) after the end of rivoceranib administration.

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A Post-treatment Follow-up visit will be conducted at 28 days (± 7 days) after the EOT for additional safety assessments. Long-term follow-ups will then occur for survival data at 12-week intervals until the subject withdraws consent from the study, lost to follow-up, end of the study or dies, whichever is sooner. More frequent intervals of survival follow-up may be performed to provide the most accurate survival data at the time of final analysis.

3.2 Study Centers

The study will be conducted at approximately 12 sites.

3.3 Randomization and Blinding

The study is open-label and non-randomized. Therefore the Investigator, site staff, and sponsor will know the treatment assignment.

3.4 Sample Size Determination

The required sample size of using ORR as the primary endpoint for the single-arm design is based on excluding 10% from the lower limit of the 95% CI. The calculation is equivalent to estimating the sample size that is significantly better than the historical 10% rate at a 5% significance level. Analysis from PASS (Version 16) shows that a sample size of 64 will achieve 90% power at a 5% significance level with the target ORR at 25% to detect the difference of 15% (=25% – 10%) using a two-sided exact binomial test. Accounting for a 10% dropout rate, 72 subjects will need to be enrolled.

3.5 Duration of Study

The maximum duration of the study is estimated to be 48 months and includes screening, treatment and follow-up phases.

3.6 Schedule of Assessments

The Schedule of Assessments (SoA) is presented in Table 2. Note that table and Appendix references in the study SoA refer to respective descriptions in the RM-202 study protocol.

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Table 2: Schedule of Assessments

Assessments	Screening Period	Treatment Period								End of Treatment / Follow-up Period			Notes
	Screening Visit	Cycle 1[a]		Cycles 2-3[a]			Cycle 4 and All Subsequent Cycles[a]			End of Treatment (EOT) (within 7 days from last dose)	Post-treatment Follow-up (28 days from EOT)	Long-term Follow-up (every 12 weeks from Post-treatment Follow-up)	
Day		D1[b]	D15	D1	D15	D28	D1	D15[c]	D28				
Visit Window (days)	-28 to -1	-	±3	±3	±3	±7	±3	±3	±7	±7	±7	±7	
Study Procedures													
Informed Consent	X												Written informed consent must be obtained **prior** to the performance of any screening procedure or study procedure.
Demographics	X												Age, sex and race/ethnicity
Medical History	X												Includes clinically significant past and current diagnoses including surgical procedures within 1 year prior to signing informed consent and any surgical procedures performed for treatment of cancer, regardless of when they were performed.
Cancer History	X												Full history of cancer including date of initial diagnosis, primary location, stage, metastatic and prior treatment information. In addition, evidence of disease progression within the 6 months prior to study entry.
Height and Weight	X	X	X	X	X		X			X	X		Measure height (without shoes) at screening only.
Physical Examination	X	X	X	X	X		X			X	X		Complete physical examinations at screening and EOT; targeted physical examinations at all other indicated visits.
Vital Signs	X	X	X	X	X		X	X		X	X		Sitting or recumbent position after at least 5 minutes, obtain blood pressure, heart rate, pulse-oximetry, respiration rate, and body temperature.

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Assessments	Screening Period	Treatment Period								End of Treatment / Follow-up Period			Notes
	Screening Visit	Cycle 1[a]		Cycles 2-3[a]			Cycle 4 and All Subsequent Cycles[a]			End of Treatment (EOT) (within 7 days from last dose)	Post-treatment Follow-up (28 days from EOT)	Long-term Follow-up (every 12 weeks from Post-treatment Follow-up)	
Day		**D1[b]**	**D15**	**D1**	**D15**	**D28**	**D1**	**D15[c]**	**D28**				
Visit Window (days)	**-28 to -1**	**-**	**±3**	**±3**	**±3**	**±7**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	
ECOG Performance Status	X	X	X	X	X		X			X	X		Refer to APPENDIX 3
Electrocardiogram	X	X[c, d]	X [c, d]	X[c]			X[c]			X			Supine or recumbent position after at least 5 minutes, single 12-lead ECG will be performed at screening and EOT, and before rivoceranib administration on D1 of C1 to C6 and D15 of C1. In addition, 12-lead ECG should be performed 3 hours +/- 30 min after rivoceranib administration on C1D1 and C1D15 to correspond with PK blood draw.
Eligibility Review	X												Eligibility will be confirmed before the subject receives the first dose of rivoceranib on C1D1.

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Assessments	Screening Period	Treatment Period								End of Treatment / Follow-up Period			Notes
	Screening Visit	Cycle 1[a]		Cycles 2-3[a]			Cycle 4 and All Subsequent Cycles[a]			End of Treatment (EOT) (within 7 days from last dose)	Post-treatment Follow-up (28 days from EOT)	Long-term Follow-up (every 12 weeks from Post-treatment Follow-up)	
Day		D1[b]	D15	D1	D15	D28	D1	D15[c]	D28				
Visit Window (days)	-28 to -1	-	±3	±3	±3	±7	±3	±3	±7	±7	±7	±7	
Tumor Assessments	X					X			X	X		X	• At screening, a CT scan of the neck, chest, abdomen and pelvis will be performed with contrast. MRI of the neck, abdomen and pelvis (MRI brain if needed) and non-contrast chest CT should be used if contrast agent is contraindicated in a subject or if determined to be clinically indicated by the Investigator. A bone scan and brain CT scan can be performed according to clinical symptoms or if subject had prior history of bone involvement or CNS involvement. Standard of care scan (even if performed before obtaining consent) may be used for the screening visit if within the visit window. • Thereafter, scans will be repeated every 8 ± 1 weeks (regardless of any dose interruptions) for the first year and then approximately every 12 ± 1 weeks (regardless of any dose interruptions) and at EOT, or as clinically indicated.

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Assessments	Screening Period	Treatment Period								End of Treatment / Follow-up Period			Notes
	Screening Visit	Cycle 1[a]		Cycles 2-3[a]			Cycle 4 and All Subsequent Cycles[a]			End of Treatment (EOT) (within 7 days from last dose)	Post-treatment Follow-up (28 days from EOT)	Long-term Follow-up (every 12 weeks from Post-treatment Follow-up)	
Day		D1[b]	D15	D1	D15	D28	D1	D15[c]	D28				
Visit Window (days)	-28 to -1	-	±3	±3	±3	±7	±3	±3	±7	±7	±7	±7	
													• Subjects who discontinue treatment for reasons other than progression will have scans at the EOT visit (unless their previous restaging was performed within 6 weeks) and every 12 ± 1 weeks thereafter (or with the standard of care restaging frequency for their disease) until initiation of a new therapy. • Imaging should be performed using the same imaging modality. All scans should be available for submission to central archiving, Investigator or Institutional assessment and Independent Central review. All the baseline scans using the same imaging modality will be repeated at each follow-up visit at above mentioned timepoints prior to scheduled assessment and dosing. At minimum, scans of neck, chest and abdomen should be performed if all scans (neck, chest, abdomen, pelvis) are not possible. Brain and bone scans will be performed as clinically indicated.
Adverse Event Evaluation	X	X	X	X	X		X	X		X	X		Monitored and documented continuously from the time the informed consent form is signed until 30 calendar days after stopping study treatment or initiation of new anticancer therapy.

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Assessments	Screening Period	Treatment Period								End of Treatment / Follow-up Period			Notes
	Screening Visit	Cycle 1[a]		Cycles 2-3[a]			Cycle 4 and All Subsequent Cycles[a]			End of Treatment (EOT) (within 7 days from last dose)	Post-treatment Follow-up (28 days from EOT)	Long-term Follow-up (every 12 weeks from Post-treatment Follow-up)	
Day		D1[b]	D15	D1	D15	D28	D1	D15[c]	D28				
Visit Window (days)	-28 to -1	-	±3	±3	±3	±7	±3	±3	±7	±7	±7	±7	
Previous/ Concomitant Medication	X	X	X	X	X		X	X		X	X		Any current medications and medications administered within 28 days prior to signing the informed consent form. Medications for treatment of cancer will be collected separately regardless of when those were administered.
Quality of Life		X[c]		X[c]			X[c]			X			Subjects will complete Functional Assessment of Cancer Therapy (FACT)-G questionnaire every 8 weeks for the first year of therapy at C1D1, C3D1, C5D1, C7D1, C9D1, C11D1, C13D1, then every 12 weeks thereafter (e.g., C16D1, C19D1, C22D1, etc.) and EOT.
Survival Status											X	X	At Post-treatment Follow-up, remind the subject of 24 months Long-term (survival) Follow-up contacts every 12 weeks until withdrawal of consent, lost to follow-up, end of the study or death, whichever occurs earlier. Death information may be obtained through a public record search if local agencies permit.
Clinical Laboratory Sample Collection													
Serological Tests	X												Serological test results obtained within 2 years prior to study enrollment may be used as standard of care measurements to satisfy the inclusion/exclusion criteria. Refer to APPENDIX 2

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Assessments	Screening Period	Treatment Period								End of Treatment / Follow-up Period			Notes
	Screening Visit	Cycle 1[a]		Cycles 2-3[a]			Cycle 4 and All Subsequent Cycles[a]			End of Treatment (EOT) (within 7 days from last dose)	Post-treatment Follow-up (28 days from EOT)	Long-term Follow-up (every 12 weeks from Post-treatment Follow-up)	
Day		D1[b]	D15	D1	D15	D28	D1	D15[c]	D28				
Visit Window (days)	-28 to -1	-	±3	±3	±3	±7	±3	±3	±7	±7	±7	±7	
Serum Chemistry	X (-14 to -1)		X	X[c]	X		X[c]	X		X	X		Fasting glucose at screening and further fasting glucose only if necessary in the opinion of the Investigator. If nonhematological treatment-related toxicity occurs, may be performed more frequently at the Investigator's discretion during the treatment period. Refer to APPENDIX 2
Clinical Hematology	X (-14 to -1)		X	X[c]	X		X[c]	X		X	X		If hematological treatment-related toxicity occurs, may be performed more frequently at the Investigator's discretion during the treatment period. Refer to APPENDIX 2
Coagulation Panel	X (-14 to -1)		X	X[c]	X		X[c]			X			Coagulation labs may be performed more frequently at the Investigator's discretion during the treatment period. Refer to APPENDIX 2
Thyroid Panel	X (-28 to -1)												Screening and as clinically indicated. Refer to APPENDIX 2
Urinalysis	X (-14 to -1)		X	X[c]	X		X[c]	X		X	X		Refer to APPENDIX 2
Pregnancy Test	X (-3 to -1)			X[c]			X[c]						For WOCBP, including women who have not been post-menopausal for at least 1 year prior to Screening Visit. Pregnancy test obtained at screening within 72 hours prior to C1D1. Serum β-hCG must be used at screening and if a urine hCG is equivocal or positive during the remainder of the study; otherwise urine hCG may be used.

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Assessments	Screening Period	Treatment Period								End of Treatment / Follow-up Period			Notes
	Screening Visit	Cycle 1[a]		Cycles 2-3[a]			Cycle 4 and All Subsequent Cycles[a]			End of Treatment (EOT) (within 7 days from last dose)	Post-treatment Follow-up (28 days from EOT)	Long-term Follow-up (every 12 weeks from Post-treatment Follow-up)	
Day		D1[b]	D15	D1	D15	D28	D1	D15[e]	D28				
Visit Window (days)	-28 to -1	-	±3	±3	±3	±7	±3	±3	±7	±7	±7	±7	
Pharmacokinetics													
Plasma		X[c, d]	X[c]	X[c]			X[c]						PK evaluations in all subjects: • C1D1 and C1D15: predose and postdose at 3h • Day 1 of all subsequent cycles: predose Intensive PK evaluations in up to 12 subjects: • C1D1 and C1D15: predose and postdose at 1h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 16h, and 24h • Day 1 of all subsequent cycles: predose Refer to Table 5
Research Sample Collection													
Tumor Markers	X												Archival tumor tissue, if available or fresh tumor samples to investigate presence of *MYB* or *MYB-L1* translocations.
Study Treatment													
Rivoceranib		→											Continuous daily dosing

Note: 1 cycle = 28 days (± 3 days)
Abbreviations: C=cycle; CNS=central nervous system; CT=computed tomography; D=day; DC=Discontinuation; ECG= electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; h=hour(s); hCG=human chorionic gonadotropin; MRI = magnetic resonance imaging; PK=pharmacokinetics; WOCBP = women of childbearing potential

[a.] If during treatment, the decision is made to interrupt the study drug treatment, the subject should be appropriately evaluated prior to resuming treatment

[b.] Cycle 1 Day 1 is designated as the Baseline visit

[c.] Procedures should be performed before rivoceranib administration

[d.] Procedures should be performed after rivoceranib administration

[e.] D15 follow-up visit will be optional for all subsequent cycles from cycle 4. The Investigator may decide to follow up every 2 or 4 weeks based on subject's clinical condition.

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[f] If the post treatment follow-up visit was not completed, the long-term follow-up will occur every 12 weeks from the EOT visit. If both EOT and posttreatment follow-up visits were not completed, the long-term follow-up will occur every 12 weeks from the last dose of study drug

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4 ANALYSIS POPULATIONS

This section defines the analysis populations to be used for the planned statistical analyses.

Table 3: Analysis Populations

Population Name	Analysis purpose	Definition
Intent-to-treat (ITT) Population	Efficacy	The intent-to-treat population will include all subjects enrolled in the study.
Safety Population	Safety	The safety population will include all subjects enrolled in the study who received any amount of rivoceranib.
Efficacy Evaluable Population	Efficacy (primary and secondary efficacy)	The efficacy evaluable population consists of eligible subjects treated with at least one dose of rivoceranib who have at least one evaluable post baseline tumor assessment.
Pharmacokinetics Population	Pharmacokinetics	PK analysis population includes all subjects who receive rivoceranib and for whom valid PK parameters can be determined.
Biomarker Population	Pharmacodynamics (exploratory endpoints)	Biomarker population includes all subjects who receive rivoceranib and have evaluable tissue samples.
Quality of Life Population	Patient-Reported Outcomes (FACT-G)	Quality of life population includes all subjects with at least one evaluable patient reported outcome.
CHOI Criteria Population	Efficacy (CHOI assessment outcomes)	The CHOI criteria population includes all eligible subjects treated with at least one dose of

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		rivoceranib who have at least baseline CT imaging with contrast and at least one evaluable post-baseline tumor assessment including CT with contrast. Note that the post-baseline tumor assessment should occur per CHOI criteria to be included in this population.
Disease Control Rate Population	Efficacy (Disease Control Rate)	The definition of disease control rate population is same as that of the efficacy evaluable population.
Interim Analysis Population	Interim Analysis Safety	The interim analysis population includes the first 48 subjects treated with rivoceranib. **Note**: For interim analysis purposes, assessments recorded through the completion of Cycle 8 (or through end of treatment period) will be considered for analysis. Additional details are provided in Appendix 2.
Interim Analysis Efficacy Population	Interim Analysis Efficacy	The interim analysis efficacy population includes subjects in the interim analysis population who have at least one post baseline tumor assessment. **Note**: For interim analysis purposes, assessments recorded through the completion of Cycle 8 (or through end of treatment period) will be considered for analysis. Additional details are provided in Appendix 2.

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5 STUDY ASSESSMENTS

This section summarizes the efficacy, safety, and PK, biomarker and Quality of Life assessments that will be performed in relation to the study objectives and endpoints described in Section 2.

5.1 Efficacy Assessments

5.1.1 Clinical Response Assessment (RECIST v1.1)

The treatment response for each subject will be determined at the time points in SoA using RECIST v1.1 guidelines. At each assessment, subjects will be assigned a treatment response by the Investigator from among the following RECIST categories:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Not Evaluable (NE)

Definitions for the above categories are summarized in Table 4 and additional information is found in Protocol Appendix 6.

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Table 4: Evaluation of Overall Assessment Using RECIST v1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
Complete response	Not evaluable [a]	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion) [a]	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion) [a]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease

a. Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

The RECIST v1.1 assessment will also be performed by Blinded Independent Central Review as per the Imaging Charter and an overall RECIST v1.1 response will be assigned. Analysis of endpoints will be performed using the Investigator or Blinded Independent Central Review assessment separately as described in Section 6 and Section 7.

Per the study Imaging Charter, the RECIST v1.1 Blinded Independent Central Review will commence with a three-reader baseline read and then two-reader on-study read that review the images independently. . If there is no discordance, the results from the first radiology read will be used. If there is discordance, an adjudication will be performed. The adjudicator will review the two primary reads and choose the read (ie., accepted read). The accepted read will be used for analysis.

5.1.2 Clinical Response Assessment (CHOI Criteria)

The Blinded Independent Central Review will also include assessment of the treatment response per the CHOI criteria. The treatment response per the CHOI criteria (CR, PR, PD, or SD) will be assigned for each time point based on the crteria below, per the study Imaging Charter.

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Table 5: Comparison of RECIST 1.1 and CHOI Tumor Response Criteria

Table 1 Comparison of RECIST 1.1 and Choi Tumor Response Criteria		
Response	**RECIST 1.1**	**CHOI†**
Complete response	Disappearance of all target lesions or lymph nodes <10 mm in the short axis	Disappearance of all target lesions; no new lesions
Partial response	>30% decrease in SLD of target lesions	≥10% decrease in tumor size or ≥15% decrease in tumor attenuation at CT; no new lesions
Progressive disease	>20% increase in SLD of target lesions with an absolute increase of ≥5 mm; new lesions	≥10% increase in SLD of lesions; does not meet the criteria for PR by virtue of tumor attenuation, new intratumoral nodules, or an increase in the size of the existing intratumoral nodules
Stable disease	None of the above	None of the above
Note. CT = computed tomography; PR = partial response; SLD = sum of longest diameters †Used for GIST.		

Per the study Imaging Charter, the CHOI Blinded Independent Central Review will be performed by two readers that will independently give an overall CHOI assessment. Adjudication will not be performed for the CHOI review.

5.1.3 Biomarker Assessments

Archival tumor tissue or fresh tumor biopsy may be used. Testing of tumor tissue samples may include but is not limited to testing for MYB and MYB-L1 locus rearrangements. Analyses will be performed at a central laboratory.

5.1.4 Patient Reported Outcome (FACT-G)

Subjects will complete a Functional Assessment of Cancer Therapy (FACT)-G questionnaire according to the planned time points provided in the SoA.

5.2 Safety Assessments

Safety assessments will consist of monitoring and recording of all AEs and serious adverse events (SAEs) using CTCAE version 5.0, laboratory evaluation, regular assessment of ECOG performance status, physical examinations and vital sign measurements; and periodic ECGs. Safety assessments will be performed according to the planned time points in the SoA.

5.2.1 Medical History

Medical history will be collected at screening. Based on findings from medical history, ongoing current conditions shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

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5.2.2 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence regardless of causal attribution in a subject administered a pharmaceutical product in a clinical trial.

Any AE that occurs after obtaining informed consent, but prior to first dose, is considered medical history unless the AE develops or worsens due to study-related procedures. All SAEs will be reported after obtaining informed consent. After initiation of rivoceranib, all AEs and SAEs will be reported until 30 calendar days after treatment with rivoceranib is stopped or until initiation of new, non-protocol specified systemic anticancer therapy, whichever occurs first.

5.2.3 Laboratory Assessments

Clinical laboratory assessments will be performed at the visits and times specified in the SoA (Table 2). The following clinical laboratory parameters will be evaluated at the times indicated.

Table 6: Laboratory Assessments and Parameters

Laboratory Assessment	Parameters
Hematology	• Absolute neutrophil count (ANC) • Hematocrit (Hct) • Hemoglobin (Hb) • Platelet count • Red blood cell (RBC) • White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Clinical Chemistry	• Alanine aminotransferase (ALT) • Albumin • Alkaline phosphatase • Amylase[a] • Aspartate aminotransferase (AST) • Bicarbonate • Blood urea nitrogen (BUN)

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	• Calcium • Chloride • Creatinine • Glucose (fasting glucose at the screening visit and further fasting glucose only if necessary in the opinion of the investigator) • Lipase[a] • Magnesium • Phosphorus • Potassium • Sodium • Total bilirubin • Total protein • Uric acid
Coagulation	• Prothrombin time (PT) or international normalized ratio (INR) • Partial thromboplastin time (PTT) or activated PTT (aPTT)
Serological	• Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus (HIV) antigen-antibody • Hepatitis B virus deeoxyribonucleic acid (HBV DNA) • Hepatitis C virus ribonucleic acid (HCV RNA)
Thyroid	• Free thyroxine (T4) • Free triiodothyronine (T3) • Thyroid stimulating hormone (TSH) • Total T4 • Total T3

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Pregnancy Testing (women of child-bearing potential)	• urine hCG • serum β-hCG (at screening only and if a urine hCG is equivocal or positive during the remainder of the study)
Urinalysis	• specific gravity • glucose, protein, occult blood, by dipstick • microscopic examination (if blood or protein is abnormal)
Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; aPTT=activated PTT; AST=aspartate aminotransferase; BUN=blood urea nitrogen; Hb=hemoglobin; HBV DNA= hepatitis B virus deeoxyribonucleic acid; hCG=human chorionic gonadotropin; Hct=hematocrit; HCV RNA= hepatitis C virus ribonucleic acid; HIV=human immunodeficiency virus; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; TSH=thyroid stimulating hormone; WBC=white blood cell. a. Only tested at screening b. Serological test results obtained within 2 years of study enrollment may be used	

5.2.4 Weight and Height

Weight and height will be measured at the times indicated in the SoA.

5.2.5 Vital Signs

Vital signs (blood pressure, temperature, heart rate, pulse-oximetry and respiratory rate) will be measured according to the SoA. Vital signs will be measured in a seated or recumbent position after at least 5 minutes rest.

5.2.6 Electrocardiograms (ECGs)

ECGs will be recorded at the specified time points and will correspond with the pharmacokinetic blood draw(s) as specified in the SoA. A single 12-lead ECG will be obtained after the subject has been in a supine or recumbent position, resting for at least 5 minutes. The following parameters will be recorded: heart rate (beats/min), QRS interval (msec), QT interval (msec), QTcF interval (msec), PR interval (msec), RR interval (msec), and overall interpretation (Normal, abnormal clinically significant, abnormal not clinically significant).

5.2.7 Physical Examinations

Physical examinations will be performed according to the SoA.

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A complete physical examination will be performed at screening, and at the end of treatment. The complete physical examination includes measurement of palpable or visible lesions (if any), as well as assessment of skin, head, eyes, ears, nose, throat, neck, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurological examination will also be performed. Weight will also be measured and recorded. Height (without shoes) will be measured and recorded at screening only.

A targeted physical examination will be performed during additional visits and will include any system that might be associated with tumor assessment and systems associated with symptom.

5.2.8 ECOG Performance Status

ECOG performance status will be assessed according to the SoA.

5.2.9 Prior and Concomitant Medications

Any current medications and medications administered within 28 days prior to signing the informed consent form will be recorded. Medications for treatment of cancer will be collected separately regardless of when those were administered.

5.3 Pharmacokinetic Assessments

Plasma concentrations of rivoceranib will be determined using a validated combined liquid chromatography-mass spectrometry method. The pharmacokinetic samples will be obtained at the times inidicated below.

Table 7: Pharmacokinetic Sampling for All Subjects

Visit	Time Points within Visit
Cycle 1 / Day 1	• Predose (<30 min predose) • 3 h +- 15 min
Cycle 1 / Day 15	• Predose (<30 min predose) • 3 h +- 15 min
Day 1 of all subsequent cycles	• Predose (<30 min predose)

In addition, intensive PK sampling will be performed for up to 12 subjects at select study sites at the following time points.

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Table 8: Intensive PK Sampling (Up To 12 Subjects)

Visit	Time Points within Visit
Cycle 1 / Day 1	• Predose (<30 min predose) • 1 h +- 15 min • 2 h +- 15 min • 3 h +- 15 min • 4 h +- 30 min • 6 h +- 30 min • 8 h +- 30 min • 10 h +- 30 min • 12 h +- 60 min • 16 h +- 60 min • 24 h +- 2 h
Cycle 1 / Day 15	• Predose (<30 min predose) • 1 h +- 15 min • 2 h +- 15 min • 3 h +- 15 min • 4 h +- 30 min • 6 h +- 30 min • 8 h +- 30 min • 10 h +- 30 min • 12 h +- 60 min • 16 h +- 60 min • 24 h +- 2 h
Day 1 of all subsequent cycles	• Predose (<30 min predose)

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6 CLINICAL OUTCOME VARIABLES

This section describes the clinical outcomes and derivation of variables considered for this study.

6.1 Primary Efficacy Endpoint

6.1.1 Objective Response Rate

The primary efficacy endpoint will be the Objective Response Rate (ORR) using RECIST v1.1 (per Investigator Assessment and Blinded Independent Central Review) based on the Efficacy Evaluable Population.

Best Overall Response (BOR) will be determined based on the overall visit responses from each RECIST assessment by the Investigator and Blinded Independent Central Review. BOR is defined as the best response (in the order of CR, PR, SD, PD, NE) a subject has had following the first dose of rivoceranib, but prior to and including progression or the last evaluable assessment in the absence of disease progression. PR/CR must be confirmed at the immediate next evaluable assessment at least 4 weeks after the response is first documented in order to be included. A CR or PR that is not confirmed will be considered as a best overall response of SD as long as the minimum duration of stable disease is met. The minimum duration of stable disease in order to be considered a best overall response will be 7 weeks (8 week assessment and allowing 1 week for the protocol-specified visit window).

Using RECIST v1.1, the ORR is defined as the proportion of subjects whose BOR is a CR or PR. The BOR and ORR will be derived using the RECIST v1.1 Investigator Response and Blinded Independent Central Review separately.

In addition, waterfall plots and spider plots will be generated to summarize the change in sum of target lesion diameters. The spider plot will be colored based on the BOR of the subjects.

Swimmer plot for Safety Population and for patients with objective response (CR/PR) per RECIST v1.1 and CHOI criteria will be generated to present the duration of treatment, first confirmed CR/PR, first progression date, and so on.

6.2 Secondary Efficacy Endpoints

6.2.1 Progression Free Survival

The following PFS endpoints are secondary endpoints for the study:

- PFS at 6 months, 12 months, and 24 months per RECIST Version 1.1 by Investigator or Institutional Assessment

- PFS at 6 months, 12 months, and 24 months per RECIST Version 1.1 by Blinded Independent Central Review

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PFS is the time from the start of treatment with rivoceranib to the first evaluation showing PD or death, whichever occurs first. Death due to any cause will be considered in the determination of PFS.

Using RECIST v1.1, PFS will be calculated as:

- PFS (days) = Date of PD or death (whichever is earlier) – first dose date of rivoceranib + 1

As appropriate, PFS may be presented in weeks or months for analysis.

In addition, a PFS sensitivity analysis may be performed which includes clinical progression as a progression event.

6.2.1.1 Censoring Rules for Progression Free Survival

The following rules will be applied for PFS.

Subjects who have neither experienced progression (i.e. an assessment of PD using RECIST v1.1) nor died at the time of analysis will be censored at the time of the last response assessment. However, if the subject has progression or dies after 2 or more missed visits, the subject will be censored at the time of the latest response assessment prior to the missed visits. In addition, subjects that do not have documented disease progression but begin subsequent anticancer therapy will be censored on the date of the last response assessment prior to the subsequent anticancer therapy.

If the subject has no evaluable visits or does not have a baseline assessment, they will be censored on Day 1 unless the death occurs within 2 visits from baseline in which case the date of death will be used in the calculation of PFS.

The definition of two missed visits will take into account the anticipated visit schedule (8 weeks for the first year and 12 weeks thereafter) as well as the protocol-defined visit window.

The PFS time will be derived based on scan/assessment dates and not visit dates to determine radiological progression. Assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied for this calculation:

- Date of progression will be determined based on the earliest of the assessment/scan dates of the component that triggered the progression (PD using RECIST).

- When censoring a subject for PFS, the subject will be censored at the latest of the assessment/scan dates contributing to a particular overall visit assessment.

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Overall RECIST visit assessments will be determined by the Investigator (or Blinded Independent Central Review) at each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

The date of censoring for PFS based on Blinded Independent Central Review using RECIST v1.1 is defined analogously.

6.2.2 Duration of Response

Duration of response (DOR) is the time from the first response of PR or CR (which is subsequently confirmed) to the first evaluation showing PD or death, whichever occurs first. Death due to any cause will be considered in the determination of DOR.

Using RECIST v1.1, DOR will be calculated as:

- DOR (days) = Date of PD, or death (whichever is earlier) – first date of confirmed PR/CR using RECIST v1.1 + 1

As appropriate, DOR may be presented in weeks or months for analysis.

In addition, a DOR sensitivity analysis may be performed which includes clinical progression as a progression event.

DOR will be derived using the Investigator Response and Blinded Independent Central Review separately.

6.2.2.1 Censoring Rules for Duration of Response

In general, the same censoring rules for duration of response will be applied as for PFS (see Section 6.2.1.1).

6.2.3 Overall Survival

The following Overall Survival (OS) endpoints are secondary endpoints for the study:

- Overall Survival at 1 year
- Overall Survival at 2 years

OS is defined as the interval from the start of study therapy to death from any cause.

OS will be calculated as:

- OS (days) = Date of death – first dose date of rivoceranib + 1

As appropriate, OS may be presented in weeks or months for analysis.

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The last date known to be alive for each individual subject may be determined using, but not limited to, the following dates recorded on the eCRF:

- AE start and stop dates
- Study treatment start and stop dates
- Laboratory assessment dates
- Dates of vital signs, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, and electrocardiogram (ECG) assessments
- RECIST assessment dates
- Start and stop dates of concomitant medications and dates of other procedures, radiation, and alternative anti-cancer therapy
- Date subject last known to be alive on long-term follow-up

Subjects that are alive at the time of database lock will be censored on the date the subject was last known to be alive.

6.2.3.1 Censoring Rules for Overall Survival

Subjects that are alive at the time of database lock or are lost to follow-up will be censored on the last date the subject was known to be alive, as described in Section 6.2.3.

6.2.4 Time to Progression

Time to progression (TTP) is the length of time from the start of treatment with rivoceranib until objective tumor progression (i.e. an assessment of PD using RECIST v1.1). At the time of analysis of TTP, any subjects who do not experience PD, including subjects who died without PD, will be censored at the date of last disease assessment.

Using RECIST v1.1, TTP will be calculated as:

- TTP (days) = Date of PD – first dose date of rivoceranib + 1

As appropriate, TTP may be presented in weeks or months for analysis.

TTP will be derived using the Investigator Response and Blinded Independent Central Review separately.

6.2.4.1 Censoring Rules for Time to Progression

The following rules will be applied for TTP.

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Subjects who have not experienced progression (i.e. an assessment of PD using RECIST) at the time of analysis will be censored at the time of the last response assessment. Further, if a subject dies in the absence of progression the subject will be censored at the time of the last response assessment.

However, if the subject has progression after 2 or more missed visits, the subject will be censored at the time of the latest response assessment prior to the missed visits. In addition, subjects that do not have documented disease progression but begin subsequent anticancer therapy will be censored on the date of the last response assessment prior to the subsequent anticancer therapy.

If the subject has no evaluable visits or does not have a baseline assessment, they will be censored on Day 1.

The definition of two missed visits will take into account the anticipated visit schedule (8 weeks for the first year and 12 weeks thereafter) as well as the protocol-defined visit window.

The TTP time will be derived based on scan/assessment dates and not visit dates to determine radiological progression. Assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied for this calculation:

- Date of progression will be determined based on the earliest of the assessment/scan dates of the component that triggered the progression (PD using RECIST).

- When censoring a subject for TTP, the subject will be censored at the latest of the assessment/scan dates contributing to a particular overall visit assessment.

Overall RECIST visit assessments will be determined by the Investigator and Blinded Independent Central Review at each assessment (scheduled or unscheduled) and will contribute to the derivation of TTP.

6.2.5 Disease Control Rate

The Disease Control Rate (DCR) is the proportion of subjects who achieve a CR, PR, or SD for ≥ 3 months from the start of treatment with rivoceranib and are confirmed with the same or better response at the immediate next evaluable tumor assessment. Three months will be defined as 90 days from the first dose of rivoceranib for purposes of calculating the DCR.

The DCR will be derived using RECIST v1.1, assessed by both Investigator and Blinded Independent Central Review Assessment separately.

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6.3 Exploratory Endpoints

6.3.1 FACT-G Questionnaire

Patient-reported outcomes for the FACT-G questionnaire will be recorded.

6.3.2 Efficacy Endpoints per CHOI Criteria

The BOR will be determined based on the overall visit responses from each CHOI assessment by the Blinded Independent Central Review. BOR is defined as the best response (in the order of CR, PR, SD, PD, NE) a subject has had following the first dose of rivoceranib, but prior to and including progression or the last evaluable assessment in the absence of disease progression. PR/CR must be confirmed at the immediate next evaluable assessment at least 4 weeks after the response is first documented in order to be included. A CR or PR that is not confirmed will be considered as a best overall response of SD as long as the minimum duration of stable disease is met. The minimum duration of stable disease in order to be considered a best overall response will be 7 weeks (8 week assessment and allowing 1 week for the protocol-specified visit window).

Using the CHOI criteria, the ORR is defined as the proportion of subjects whose BOR is a CR or PR.

Besides ORR analysis, DCR, PFS, DOR and TTP using CHOI criteria will be analyzed based on the CHOI Criteria Population.

6.4 Safety Endpoints

6.4.1 Adverse Events

A Treatment-emergent adverse event (TEAE) is defined as an adverse event occurring on or after the first dose of rivoceranib until 30 days after the last dose date of rivoceranib or initiation of other anticancer therapy (whichever is earlier). Pre-treatment AEs that worsen in severity after first dose of rivoceranib will be considered TEAEs. Any AEs occurring more than 30 days after the last dose date of study drug considered related to study drug will be considered TEAEs.

The severity of AEs will be graded by the Investigator using the Common Terminology Criteria for Adverse Events (version 5.0). Further details regarding the CTCAE grade are provided in study protocol Appendix 7. AEs will be coded using the Medical Dictionary for Regulatory Activities (Version 23.1 or higher) as described in the Data Management Plan.

The relationship of each AE to rivoceranib will be assessed by the Investigator according to the following criteria.

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Table 9: Adverse Event Relationship to Rivoceranib

Relationship Category	Description
Not related	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of rivoceranib; or, a causal relationship to the study treatment is considered implausible
Unlikely related	The current knowledge or information about the AE indicates that a relationship to the study treatment is unlikely.
Possibly related	There is a clinically plausible time sequence between onset of the AE and administration of the study treatment, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the study treatment is one of several plausible AE causes.
Related	The AE is clearly related to use of the study treatment.

For purposes of table summaries for related AEs, AEs considered related or possibly related to rivoceranib by the Investigator will be summarized

6.4.2 Exposure to Rivoceranib

The duration of rivoceranib treatment will be calculated as:

- Duration of rivoceranib treatment (days) = last dose date of rivoceranib – first dose date of rivoceranib + 1

The number of doses of rivoceranib will be calculated as:

- Number of doses of rivoceranib = last dose date of rivoceranib – first dose date of rivoceranib – cumulative days of dose interruptions + 1

The duration of a dose interruption is defined as:

- Duration of dose interruption = End date of interruption – Start date of interruption + 1

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The cumulative days of dose interruptions is defined as the sum of the duration of dose interruptions during the treatment period. If a drug interruption is recorded after the last dose date of rivoceranib (e.g. drug is interrupted and then later discontinued) then it will not be included in derivation of the number of doses of rivoceranib.

If start/stop dates of dosing are missing after querying, the duration of treatment interruption will be treated as 1 day.

The cumulative dose of rivoceranib in milligrams will also be derived from the number of doses of rivoceranib by summing the daily dose of rivoceranib during the treatment period.

Relative dose intensity (RDI) is the percentage of actual cumulative doses of rivoceranib administered relative to the intended doses planned through to treatment discontinuation.

RDI will be calculated as follows:

- RDI = 100% x d/D

where d (mg) is actual cumulative doses administered and D (mg) is cumulative doses planned. D is the total dose that would be administered, assuming 700 mg once daily.

Actual dose intensity (ADI) is the actual cumulative doses of rivoceranib administered relative to the duration of rivoceranib treatment.

6.4.3 Prior and Concomitant Medications

Prior medications are medications that were started and stopped prior to the first dose of rivoceranib. Concomitant medications are medications that were taken on or after the first dose date of rivoceranib.

Prior and concomitant medications will be coded using the WHO Drug Dictionary (Version Version B3 September 2020 as specified in the Data Management Plan).

7 STATISTICAL ANALYSES

This section describes the statistical analyses to be conducted in relation to the primary, secondary, and exploratory objectives of the study.

7.1 General Statistical Considerations

All analyses will be performed using SAS® Version 9.3 or higher.

Unless specified otherwise, the analyses of data collected will be descriptive and summaries will be presented in total for the specified analysis population. Statistical analyses will be purely descriptive and no formal hypothesis testing or comparative analyses will be performed. Confidence intervals (CIs) will be constructed at the 95% confidence level where appropriate.

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For continuous variables, the number of observations (n), mean, standard deviation, median, minimum, and maximum will be provided as summary statistics. For categorical variables, the frequency and percentage in each category will be displayed.

Summary tables will in general present all subjects in a given analysis population.

Efficacy analyses will in general be based on the Efficacy Evaluable Population, and the OS endpoint will be analyzed based on the ITT Population. Additional exploratory analyses may be presented using other study populations (e.g. CHOI Criteria Population).

Safety analyses will be performed using the Safety Population.

Subject characteristics data will be summarized for the Safety Population. If the Safety Population differs from other defined analysis populations, additional subject characteristic summaries may be generated using the other analysis populations.

Comprehensive by-subject data listings will be generated.

If applicable, additional descriptive summaries may also be produced in order to better characterize the data or study population.

7.1.1 Baseline Definition

Unless stated otherwise, the baseline value is defined as the last non-missing measurement prior to the first dose of rivoceranib.

Study Day 1 will be considered as the date of the first dose of rivoceranib.

7.1.2 Covariate Adjustment

No adjustment for other covariates is planned.

7.1.3 Multicenter Studies

The center effect will not be considered for this study.

7.1.4 Multiple Comparisons

No multiple comparisons adjustment will be applied to the efficacy analysis.

7.1.5 Handling of Dropouts or Missing Data

Unrecorded data values will be recorded as missing. Only recorded (i.e. complete) data values will be used for statistical analyses. In general, invalid or missing values will not be imputed unless stated otherwise.

In cases of missing or incomplete dates (e.g. AEs and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing,

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will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original eCRFs will be presented in the data listings.

To be conservative in the case of missing causality assessment for AEs after data querying, AEs will be assumed to be related to study drug. If the CTCAE grade is missing after data querying it will not be imputed and the subject will be presented in table summaries based on the maximum CTCAE grade of all other recorded AEs meeting applicable criteria.

For subjects lost to follow-up or with missing RECIST assessments, censoring rules for efficacy endpoints are defined in Section 6.

7.1.6 Subgroup Analyses

Subgroup analyses may be performed for all efficacy endpoints including, but not limited to, subjects that have not been treated with prior VEGF inhibitor treatment (i.e. VEGF inhibitor-naïve), and VEGF inhibitor-treated subjects as defined below.

Table 10: VEGF Inhibitor-Naïve and VEGF Inhibitor-treated Subjects Definition

Analysis Subgroup	Description
VEGF inhibitor-naïve	• All subjects in a given analysis population not meeting the definition of VEGF inhibitor-treated at the time of enrollment
VEGF inhibitor-treated	All subjects with any prior cancer treatment with preferred term matching any preferred term in the WHO Drug Dictionary standardized drug grouping term “Antiangiogenic drugs with antagonistic effect on the VEGFR, inhibiting actions of VEGF or VEGFR TKs” (full list in Appendix 1)

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7.1.7 Interim Analysis

Interim analysis may be performed after approximately 48 subjects either discontinue the study treatment or complete C8D28 tumor assessments (around week 32).

The interim analysis will include the following descriptive analyses.

Table 11: Scope for Interim Analysis

Analysis Category (Population)	Description
Subject Characteristics (Interim Analysis Population)	• Subject disposition • Demographics • Cancer history • Prior cancer therapies • Prior cancer surgeries and radiation • Exposure to rivoceranib
Safety (Interim Analysis Population)	• Treatment-Emergent Adverse Events (TEAEs), TESAEs, and TEAEs related to rivoceranib by System Organ Class (SOC), Preferred Term (PT), and Maximum CTCAE grade • CTCAE Grade 3 and higher TEAEs by SOC and PT • SAEs by SOC and PT • AEs leading to dose reduction, interruption, or discontinuation of rivoceranib by SOC and PT • Laboratory parameters (serum chemistry and hematology) and change from baseline over time • Electrocardiogram parameters and change from baseline over time • Vital Signs parameters and change from baseline over time

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Efficacy (Interim Analysis Efficacy Population)	The primary analysis of ORR by the following criteria: - Per RECIST v1.1 by investigator/institutional assessment - Per RECIST v1.1 by Blinded Independent Central Review In addition, the following secondary and exploratory will be included in this analysis: - PFS (per RECIST v1.1, using Investigator assessment and Blinded Independent Central Review) - TTP (per RECIST v1.1, using Investigator assessment and Blinded Independent Central Review) - DOR (per RECIST v1.1, using Investigator assessment and Blinded Independent Central Review) - DCR (per RECIST v1.1, using Investigator assessment and Blinded Independent Central Review) - ORR Per CHOI criteria by Blinded Independent Central Review **Note**: the above analyses will present results also for VEGF inhibitor-naïve and VEGF inhibitor-treated subgroups Additional figures including a waterfall plot and spider plot presenting the maximum change in RECIST v1.1 Sum of Target Lesion Diameters will be generated.

In addition, listings will be generated in support of the above analyses.

In general, tables and figures will be based on data collected through the end of Cycle 8 assessments for assessments specified in Appendix 2 (or all on-study assessments for subjects discontinued from treatment prior to Cycle 9). Efficacy endpoints will be calculated using all assessments up to and including assessments performed during Cycle 8 (e.g. including Cycle 8 Day 28/Week 32 RECIST assessments). In general, listings will present the same assessments summarized in tables/figures, for example, this will not include data collected after completion of Cycle 8 if this information is not summarized in summary tables or figures.

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Assessments or data points occurring after the Cycle 8 Day 28/Week 32 timepoint will not be included in listings for applicable assessments specified in Appendix 2. The format of tables, listings, and figures generated for the Interim Analysis will be specified in a standalone Interim Analysis Programming Specification.

7.1.8 COVID-19

No imputation of missing data as a result of the COVID-19 pandemic is planned for the interim analysis.

A sensitivity analysis may be performed to investigate the relationship between COVID-19 and safety and/or efficacy data. For example, a sensitivity analysis may be performed excluding a subject(s) with multiple major protocol deviations related to COVID-19 in order to assess the impact on the safety and/or efficacy analysis. In the event this occurs, further details including the subject(s), assessment(s) affected, and results will be described in an analysis plan amendment and/or the clinical study report (CSR) and will include but not be limited to.

- Listings and/or summary tables to summarize the impact of COVID-19: AEs, deaths, protocol deviations.
- Listing of missing or incomplete tumor imaging due to COVID-19.

Applicable data collected in relation to COVID-19 on the eCRF will be summarized as appropriate and/or included in data listings.

Protocol deviations resulting from COVID-19 will be recorded and included in the protocol deviation listing and in a separate listing.

7.2 Study Population Data

7.2.1 Subject Disposition

Subject disposition will be summarized for all screened subjects.

The following subject disposition categories will be summarized:

- Subjects screened;
- Subjects enrolled in the study and by country (US and South Korea);
- Subjects treated with rivoceranib;
- Subjects discontinued from study treatment;
- Subject survival status at last follow-up visit; and
- Subjects who terminated the study.

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For subjects who discontinued study treatment and subjects who terminated the study, a summary will be provided by reason for discontinuation or termination.

The total number of subjects in each defined analysis population will be tabulated. The analysis populations will be listed.

Subject disposition data will be listed by subject.

7.2.2 Protocol Deviations

Protocol deviations considered reportable in the CSR per the study. Protocol Deviation Plan will be listed by subject. Descriptions and categories of CSR-reportable protocol deviations (major protocol deviations) are found in the Protocol Deviation Plan. The relationship of protocol deviations to COVID-19 will be recorded in the PD log and included in the listing.

7.2.3 Demographics and Cancer History

Descriptive summaries of demographic and cancer history will be presented for the Safety Population.

Demographic characteristics include, but are not limited to: age, sex, childbearing potential, race, ethnicity, body weight, height, and body mass index (BMI), and baseline ECOG score.

Continuous variables including time from original cancer diagnosis to first dose date (months) and time from current cancer disagnosis to first dose date (months) will be summarized with descriptive statistics. Categorical variables including original stage, current stage, grade, and tumor location (primary site of disease, metastatic sites and time from most recent recurrence/relapse to first dose date) will be summarized.

The primary tumor locations will be summarized per below catergories:

- Major salivary glands;
- Minor salivary glands;
- Other.

Demographic and cancer history data will be presented in a by-subject listing.

7.2.4 Medical History

The reported medical history terms will be coded using the MedDRA v23.1 (or higher as described in the Data Management Plan) and presented in a summary table by SOC and PT for the Safety Population. Subjects may have more than one reported medical history event for each SOC and PT but will be only counted once within each SOC and PT classification.

Reported medical history data will be presented in a by-subject listing.

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7.2.5 Prior Cancer Therapies

The number of lines of prior systemic cancer therapy and reason for discontinuation of any prior cancer therapy treatment will be summarized. The minimum, maximum and median of the lines of prior systemic cancer therapy will be provided. Prior chemotherapy and prior VEGF inhibitor-directed therapy will be summarized separately. A listing of all prior systemic therapies will be provided.

The reported cancer therapy/medication terms will be coded using WHO Drug Dictionary (Version B3 September 2020 as described in the Data Management Plan). Prior cancer therapies/medications will be summarized by Anatomical Therapeutic Chemical (ATC) and Preferred Name (PN) A subject will be counted only once within an ATC classification but may contribute to two or more preferred name in the same classification.

The number of subjects with prior radiation therapy or prior cancer surgery will be summarized. The radiotherapy site or region and the amount of radiation will be summarized. In addition, the time from last VEGF inhibitor therapy to the first dose of study drug and the number of prior VEGF inhibitor therapies will be summarized.

Prior cancer therapies, radiation therapy, surgery and prior VEGF inhibitor therapies will be presented in a by-subject litsing.

7.2.6 Evidence of Disease Progression Prior to Study

The evidence of diease progression based on the eCRF page prior to study enrollment per below categories will be summarized for all enrolled subjects:

a) At least a 20% increase in radiologically or clinically measureable lesions;

b) Appearance of any new lesions only;

c) Both a and b.

For subjects who meeting criteria a, the below analyses will be performed:

1) Summarize the maximum change in sum of target lesions diameters from pre-study baseline to pre-study which was assessed within 6 month prior to study enrollment;

2) Summarize the maximum change in sum of target lesions diameters from pre-study to best response during first 6 month on treatment;

3) Summarize the maximum change in sum of target lesions diameters from pre-study to best response on treatment;

By taking on-study baseline as a reference, the following additional analyses will be performed:

4) Summarize the maximum change in sum of target lesions diameters from pre-study baseline to on-study baseline;

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5) Summarize the maximum change in sum of target lesions diameters from on-study baseline to best response during first 6 month on treatment;

6) Summarize the maximum change in sum of target lesions diameters from on-study baseline to best response on treatment;

Paired T-test will be used to compare the maximum changes of the sum of targer lesions diameters between items 2 vs. 1, 3 vs. 1 , 5 vs. 4 and 6 vs. 4.

Waterfall plot which presents the percent change of sum of target lesions diameters from pre-study baseline to on-study baseline will be provided for subjects who meet criteria a as adhoc analysis. Spider plot from pre-study baseline through the end of treatment will be presented.

7.3 Efficacy Analyses

Efficacy analyses described in this section will be performed using the Efficacy Evaluable Population except for OS which will be analyzed using ITT Population.

A by-subject listing of BOR, DoR, DCR, PFS, OS, and TTP derived endpoints will be presented. In addition, a by-subject overall response assessments will be presented for Efficay Evaluable Population and for patients with unconfirmed CR/PR per RECIST v1.1 by Investigator, respectively. For patients with confirmed CR/PR per RECIST v1.1 by Investigator, the dates of first dose and last dose of study drug, the date of first confirmed CR/PR, and the date of last scan, and date of progression will be included in one by-subject listing. If patients continue treatment beyond progression, the patients will be listed also.

Summaries will be performed for the overall population and for the VEGF inhibitor-naïve and VEGF inhibitor-treated populations. Additional summaries may be provided for subjects with and without any prior systemic therapy, and as a sensitivity analysis, the summaries will be provided for populations with and without any prior systemic therapy excluding VEGF inhibitor-treated patients. Summaries will be performed by US and South Korea.

Sensitivity analyses may be conducted for all the efficacy endpoints. These are as follows:

- Excluding subjects with major protocol deviations.
- Including subjects with unconfirmed CR or PR as a responder as last assessment available, which includes subjects just before censoring and subjects with unconfirmed CR or PR then missing scan(s) due to COVID-19.

7.3.1 Primary Efficacy Analyses

The primary efficacy analysis will present the ORR. The point estimate of the ORR along with the exact Clopper-Pearson 95% CI will be presented. Subjects who do not have sufficient baseline and on-study tumor assessments to characterize response (i.e. who have a

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BOR of NE) will be included as non-responders in the primary analysis calculation of the ORR.

The BOR will also be tabulated to show the number and percentage of subjects in each response category.

This analysis will be performed separately for both the Investigator RECIST v1.1 response and Blinded Independent Central Review RECIST v1.1 response.

Dose level at the time of achieving confirmed CR/PR per RECIST v1.1 by Investigator will be summarized. The time to objective response from the first dose of study drug will be summarized per RECIST v1.1 by Investigator and Blinded Independent Central Review and CHOI criteria by Blinded Independent Central Review.

7.3.2 Secondary Efficacy Analyses

7.3.2.1 Progression Free Survival

PFS will be estimated using the Kaplan-Meier method for the Efficacy Evaluable Population.

The number and percentage of subjects experiencing a PFS event and the type of event (RECIST progression or death), subjects censored and the reason of censoring will be summarized. The Kaplan-Meier estimate of the median PFS, 25th and 75th percentiles will be summazied and Brookmeyer-Crowley 95% CI of median PFS will be presented (Brookmeyer and Crowley 1982). In addition, the 95% CI for the number of subjects progression-free at clinically significant time points (e.g. 6 months, 9 months, 12 months, 18 months, 2 years, etc.) will be summarized.

Kaplan-Meier plots of PFS will be presented.

This analysis will be performed separately for both the Investigator RECIST v1.1 response and Blinded Independent Central Review RECIST v1.1 response.

7.3.2.2 Duration of Response

DOR will be estimated using the Kaplan-Meier method for the Efficacy Evaluable Population.

The number and percentage of subjects experiencing a DOR event and the type of event (RECIST progression or death),subjects censored and the reason of censoring will be summarized. The Kaplan-Meier estimate of the median DOR, 25th and 75th percentiles will be summazied and Brookmeyer-Crowley 95% CI of median DOR will be presented (Brookmeyer and Crowley 1982). In addition, the 95% confidence interval for the number of subjects with durable response at clinically significant time points (e.g. 6 months, 9 months, 12 months, 18 months, 2 years etc.) will be summarized.

Kaplan-Meier plots of DOR will be presented.

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This analysis will be performed separately for both the Investigator RECIST v1.1 response and Blinded Independent Central Review RECIST v1.1 response.

7.3.2.3 Overall Survival

OS will be estimated using the Kaplan-Meier method for the ITT Population .

The number and percentage of deaths and subjects censored will be summarized. The Kaplan-Meier estimate of median OS, 25th and 75th percentiles will be summazied and Brookmeyer-Crowley 95% CIof median OS will be presented (Brookmeyer and Crowley 1982). In addition, the 95% CI for the number of subjects alive at clinically significant time points (e.g. 12 months, 24 months, etc.) will be summarized.

Kaplan-Meier plots of OS will be presented.

The analysis of OS use all follow-up assessments (including unscheduled) as well as data available from other assessments as described in Section 6.2.3.

The study follow-up will be analyzed using reverse Kaplan-Meier method. The 25th, 75th, and median and 95% CI of study follow up will be summarized. In addition, the minimum and maximum will be presented.

7.3.2.4 Time to Progression

TTP will be estimated using the Kaplan-Meier method for the Efficacy Evaluable Population.

The number and percentage of subjects experiencing a TTP event, subjects censored and the censoring reason will be summarized. The Kaplan-Meier estimate of the median TTP, 25th and 75th percentiles will be summazied and Brookmeyer-Crowley 95% CI of median TTP will be presented (Brookmeyer and Crowley 1982). In addition, the 95% CI for the number of subjects with no progression at clinically significant lengths of time (e.g. 6 months, 9 months, 12 months, 18 months, 2 years, etc.) will be summarized

Kaplan-Meier plots of TTP will be presented.

This analysis will be performed separately for both the Investigator RECIST v1.1 response and Blinded Independent Central Review RECIST v1.1 response.

7.3.2.5 Disease Control Rate

The DCR determined by Investigator and Blinded Independent Central Review Assessment per RECIST v1.1 will be presented along with the exact Clopper-Pearson 95% CI. Subjects who do not have sufficient baseline and on-study tumor assessments to characterize response (i.e. who have a BOR of NE) will be included as failures in the calculation of the DCR.

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7.4 Exploratory Efficacy Analyses

7.4.1 Efficacy Analyses per CHOI Criteria

The efficacy analyses using CHOI criteria will be based on the CHOI Criteria Population.

The ORR per CHOI criteria will be summarized including point estimate of the ORR along with the exact Clopper-Pearson 95% CI will be presented. The BOR will also be tabulated to show the number and percentage of subjects in each response category. The time to objective response per CHOI criteria will be summarized, including median. Besides ORR analysis, the efficacy endpoints DCR, PFS, DOR and TTP will be analyzed per CHOI criteria.

In addition, the swimmer plot, Kaplan-Meier plots of PFS compring objective response (PR or CR) vs. non-objective response will be presented. Kaplan-Meier plots of PFS in patients with $\leq$1 prior line of treatment vs $\geq$2 prior lines of treatment per RECIST v1.1 by both Investigator and Blinded Independent Central Review and per CHOI criteria will be presented.

A shift table presenting the difference of BOR per RECIST v1.1 and CHOI criteria by Blinded Independent Central Review will be presented. Patients with confirmed CR/PR per RECIST v1.1 by Investigator and Blinded Independent Central Review will be listed.

7.4.2 FACT-G Questionnaire

The FACT-G Questionnaire assessment responses will be summarized descriptively and the change from baseline will be summarized at each time point

FACT-G Questionnaire assessments will be listed by subject.

7.4.3 Biomarker Analysis

Exploratory efficacy analyses will in general be based on the Biomarker Population or a specified subset (e.g. excluding subjects that do not have a valid assessment). The number and percentage of subjects with detected MYB or MYB-L1 will be summarized. Similar to subgroup analysis on the efficacy endpoints in Section 7.3, summaries will be performed for the overall population and for the MYB-Detected and MYB-Undetected populations. Additional summaries will be performed for the overall population and for the MYBL1-Detected and MYBL1-Undetected populations. Biomarker data will be listed.

7.5 Safety Analyses

The assessment of the incidence of adverse events during the course of the study will consist of the surveillance and recording of adverse events (AEs), including serious adverse events (SAEs). Safety will also be assessed through clinical laboratory evaluations,

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immunogenicity assessments, vital signs, ECGs, physical examinations, ECOG performance status, and concomitant medication reporting.

Summaries will be tabulated in total for the Safety Population.

7.5.1 Extent of Exposure

Descriptive statistics will be provided for the total exposure, actual exposure to study drug, and cumulative dose.

The number and percentage of subjects initiating a given number of treatment cycles of study drug will be summarized (e.g. 1 cycle, 2 cycles, etc.). A cycle will be defined as 4 weeks. In addition, the number of subjects with a dose reduction or dose interruption during the treatment period will be summarized along with the reason for dose reduction or dose interruption.

The duration of rivoceranib administered at different dose levels (e.g. 700mg, 500 mg, etc.) will be summarized for the Safety Population and for patients with objective response (CR/PR) per RECIST v1.1, separately. In addition, the time of dose reduction from high dose level to lower dose level (e.g. from 700 mg to 500 mg), the time to first dose reduction, the relative and actual dose intensity will be summarized. Moreover, the percentage of patients of with number of dose reductions (e.g. 1, 2, etc.) will be summarized.

Drug exposure data will be presented in a by-subject listing. The duration of rivoceranib administered at different dose levels for patients with objective response will be presented in a by-subject listing.

7.5.2 Adverse Events

Summaries of adverse events will be presented in total for the Safety Population.

An overview of treatment-emergent adverse events will be provided which summarizes the subject incidence of the following for the Safety Population. This overview will include the number and percentage of subjects with:

- Any TEAEs;
- CTCAE Grade ≥3TEAEs;
- Serious adverse events (SAEs);
- Treatment-emergent SAEs (TESAEs),
- TEAEs with outcome of death;
- Drug-related TEAEs;
- Drug-related CTCAE Grade ≥3TEAEs;

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- Drug-related SAEs;
- TEAEs leading to dose interruption of rivoceranib;
- TEAEs leading to dose reduction of rivoceranib;
- TEAEs leading to discontinuation of rivoceranib;
- Adverse Events of Special Interest (AESI)
    - Additional information about AESI is found in Appendix 3.

The number and percentage of subjects with TEAEs will be tabulated by the highest CTCAE Grade, SOC, and PT. TEAEs related to rivoceranib, leading to dose reductions, dose interruption, discontinuation of rivoceranib will be summarized in the same manner.

AESIs will be summarized by SMQ, PT overall and by highest CTCAE grade.

TEAEs will also be summarized by SOC in descending order and PT in descending order within SOC. CTCAE Grade ≥3TEAEs, TESAEs, TEAEs with outcome of death, drug-related TEAEs, drug-related CTCAE Grade ≥3TEAEs, drug-related TESAEs, TEAEs leading to drug interruption of rivoceranib, TEAEs leading to dose reduction of rivoceranib, and TEAEs leading to discontinuation of rivoceranib will be summarized in the same manner.

TEAEs will also be summarized in by PT in descending order. The CTCAE Grade 3/4 TEAEs, drug-related TEAEs will be summarized in same manner.

For all above summaries, subjects with multiple AEs will be counted only once per SOC and PT.

Listings will be presented for TEAEs, SAEs, TEAEs leading to drug interruption, TEAEs leading to dose reduction,TEAEs leading to discontinuation of rivoceranib, , and TEAEs with outcome of death.

7.5.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be summarized using descriptive statistics for selected laboratory parameters (e.g. clinical chemistry, hematology, coagulation, urine protein) including absolute measurements and changes from baseline by scheduled time of evaluation. Changes from baseline by scheduled time of evaluation will include last visit on-study (End of Therapy Visit), maximum post-treatment value, and minimum post-treatment value. Both scheduled and unscheduled post-treatment visits will be considered for the summaries of the maximum and minimum post-treatment values.

Abnormal laboratory results will be graded according to NCI-CTCAE version 5 as applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. For select parameters (e.g. glucose), separate shift tables indicating hyper–

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and hypo-directionality of change may be produced. Both scheduled and unscheduled post-treatment visits will be considered in tabulation of the worst post-treatment value.

The abnormal laboratory results below or above the normal ranges will be summarized by time point. The shift table of urine protein will be provided.

Clinical laboratory evaluations will be listed by subject and values below or above the normal range values will be flagged.

7.5.4 Vital Signs

Descriptive statistics will be provided by time point for vital signs measurements (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and weight). Changes from baseline by scheduled evaluation, and maximum and minimum post-treatment values will be presented. Both scheduled and unscheduled post-treatment values will be considered for summaries of the minimum and maximum.

The number and percentage of subjects with the following potentially abnormal vital signs at any post-baseline visit will be summarized:

- Heart rate < 50 bmp or >120 bpm
- Heart rate increase >30 bpm or decrease >30 bpm from baseline
- Systolic blood pressure <95 mmHg or >180 mmHg
- Systolic blood pressure increase >30 mmHg or decrease >30 mmHg from baseline
- Diastolic blood pressure <50 mmHg or >110 mmHg
- Diastolic blood pressure increase >20 mmHg or decrease >20 mmHg from baseline

Vital signs assessments will be presented in a by-subject listing.

7.5.5 Electrocardiograms

Continuous ECG parameters (PR, RR, QRS, QT, QTcF) will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation and the maximum post-treatment value. Both scheduled and unscheduled post-treatment values will be considered for summaries of the maximum post-treatment values.

In addition, the incidence of the following QT and QTcF changes will be summarized by scheduled time and overall:

- Increase from baseline QTcF > 30 msec to ≤ 60 msec
- Increase from baseline QTcF > 60 msec
- Increase from baseline QT > 30 msec

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- Increase from baseline QT > 60 msec

The number and percentage of subjects with the following criteria will be summazied by scheduled time:

- QT ≥450 msec and QT <480 msec
- QT ≥480 msec and QT <500 msec
- QT ≥500 msec
- QTcF ≥450 msec and QTcF <480 msec
- QTcF ≥480 msec and QTcF <500 msec
- QTcF ≥500 msec

The overall interpretation (normal, abnormal clinically significant, abnormal not clinically significant) will be summarized by scheduled time.

A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline value, will be provided for QT and QcF: < 450 msec; ≥ 450 msec and ≤ 480 msec; > 480 msec and ≤ 500 msec; and > 500 msec.

All on-treatment ECG readings, including unscheduled assessments, will be considered in derivation of the above categories.

ECG assessments will be presented in a by-subject listing.

7.5.6 Physical Examinations

Physical examination results will be presented in a by-subject listing.

7.5.7 ECOG Performance Status

For subjects with ECOG performance status assessments, the performance status at each visit on study and worst post-baseline assessment will be presented. Both scheduled and unscheduled visits will be considered in determination of the worst post-baseline assessment. A shift table of ECOG performance status, presenting the 2-way frequency tabulation for baseline and the worst post-baseline, will be provided.

ECOG performance status results will be presented in a by-subject listing.

7.5.8 Concomitant Medications

Use of prior and concomitant medications will be summarized by ATCand PNfor the Safety Population, separately. Each subject will be counted only once within each ATC and PN. A subject may contribute to multiple preferred terms within the same ATC category. Number of subjects requiring concomitant antihypertensive therapy will be summarized.

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Prior and concomitant medications will be listed.

7.5.9 Other Safety Assessments

Results from other safety assessments (e.g. pregnancy test) may be presented in by-subject listings if applicable.

7.6 Pharmacokinetic Analysis

PK analysis, PK concentration results and methods for determination of PK parameters will be described in a standalone PK analysis plan.

8 GENERAL INFORMATION

8.1 Statistical Software

The creation of analysis datasets and statistical analyses will be done using SAS® version 9.3 or higher. The Medpace standard operating procedures (Medpace Standard Operating Procedures GL-DS-02-S4 and GL-DS-03-S3, or newest version at the time of analysis if applicable) will be followed for the validation of all SAS programs and outputs.

8.2 Format of Tables, Listings, and Figures

The format of tables, listings, and figures will be described in a stand-alone programming specifications document. The programming specification document will be prepared before database lock (or interim data lock for analyses presented at interim analysis).

9 CHANGES FROM PROTOCOL-SPECIFIED ANALYSIS

The definition of Duration of Response and corresponding summaries were clarified from protocol Section 8.3.1. The DOR will be defined as a time-to-event endpoint and summarized using Kaplan-Meier methods as described in Section 7.3.2.2.

VEGF inhibitor-treated and VEGF inhibitor-naïve subgroups were defined for efficacy analyses. Additional information is found in Section 7.1.6 and Appendix 1.

The Interim Analysis Population and Interim Analysis Efficacy Population definitions were added in order to characterize the subjects populations included in the pre-planned interim analysis.

9.1 Changes from SAP Version 1.0

- In Section 2, compared to protocol amendment 4 dated 22 October 2020, the exploratory objectives and exploratory endpoints related to ORR and DCR were

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changed.In the latest version, the ORR,DCR, PFS, DOR, and TTP based on CHOI data are the exploratory efficacy endpoints.

- In Section 4, the ITT Population was defined and will be used to analyze overall survival. The definition of Efficacy Evaluable Population and CHOI Criteria Population were revised.
- In Section 5.1.1, the reading paradigm was updated per Blinded Imaging Review Charter.
- In Section 6.4.2, added the calculation formula of relative dose intensity and actual dose intensity, and updated Section 7.5.1 accordingly.
- Section 6.2.5 was added to be consistent with the objectives and endpoints of Table 1 of Section 2.
- In Section 7.1.8, the COVID-19 related analyses were described.
- In Section 7.2.3, the summary methods of primary tumor location was added.
- Added Section 7.2.6 to discuss progression evidence prior to study enrollment and during treatment.
- In Section 7.3, added the subgroup analysis and sensitivity analysis. Section 7.3.2.5 was added to be consistent with the endpoints and ojectives on Table 1 of Section 2. In Section 7.4.1.2, added the language that the primary and secondary endpoints were to be reassessed per CHOI criteria.
- In Section 7.5.1, the summary methods of AESI, TEAEs by PT and AEs leading to dose reduction were added.
- The summary methods of abnormal laboratory results, abnormal vital signs and abnormal ECG parameters were described. The shift tables of urine protein, ECG parameters and ECOG were added.

10 REFERENCES

Brookmeyer, R., & Crowley, J. (1982). A confidence interval for the median survival time. *Biometrics*, 29-41.

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11 APPENDIX 1: ANTI-VEGF THERAPY DEFINITION

The following list of preferred terms will be used in the determination of subgroups of subjects that are VEGF inhibitor-naïve or VEGF inhibitor-treated. Additional details are provided in Section 7.1.6.

Table 12: WHO Drug Dictionary Preferred Terms for VEGF InhibitorTreatments

Preferred Term
ABT 510
AFLIBERCEPT
AFLIBERCEPT BETA
AFLIBERCEPT;CALCIUM FOLINATE;FLUOROURACIL;IRINOTECAN HYDROCHLORIDE
AFLIBERCEPT;FLUOROURACIL;FOLINIC ACID;IRINOTECAN
ALACIZUMAB PEGOL
ALTIRATINIB
ANLOTINIB
ANLOTINIB DIHYDROCHLORIDE
APATINIB
APATINIB MESYLATE
ASCORBIC ACID;BENDAZOL HYDROCHLORIDE;OGLUFANIDE DISODIUM
ASCORBIC ACID;BENDAZOL;OGLUFANIDE
ASCORBIC ACID;BENDAZOL;OGLUFANIDE DISODIUM
AXITINIB
BAT 1706
BEVACIZUMAB
BEVACIZUMAB AWWB
BEVACIZUMAB BETA
BEVACIZUMAB BVZR

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BEVACIZUMAB;CALCIUM FOLINATE;FLUOROURACIL;IRINOTECAN HYDROCHLORIDE
BEVACIZUMAB;CALCIUM FOLINATE;FLUOROURACIL;OXALIPLATIN
BEVACIZUMAB;CAPECITABINE
BEVACIZUMAB;CAPECITABINE;IRINOTECAN
BEVACIZUMAB;CAPECITABINE;IRINOTECAN HYDROCHLORIDE
BEVACIZUMAB;CAPECITABINE;MITOMYCIN
BEVACIZUMAB;CAPECITABINE;OXALIPLATIN
BEVACIZUMAB;CAPECITABINE;TEMOZOLOMIDE
BEVACIZUMAB;CARBOPLATIN
BEVACIZUMAB;CARBOPLATIN;GEMCITABINE
BEVACIZUMAB;CARBOPLATIN;PACLITAXEL
BEVACIZUMAB;CARMUSTINE
BEVACIZUMAB;CETUXIMAB
BEVACIZUMAB;DOCETAXEL
BEVACIZUMAB;ETOPOSIDE
BEVACIZUMAB;FLUOROURACIL;FOLINIC ACID
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BEVACIZUMAB;FLUOROURACIL;FOLINIC ACID;IRINOTECAN;OXALIPLATIN
BEVACIZUMAB;FLUOROURACIL;FOLINIC ACID;OXALIPLATIN
BEVACIZUMAB;FOTEMUSTINE
BEVACIZUMAB;GEMCITABINE
BEVACIZUMAB;GEMCITABINE HYDROCHLORIDE
BEVACIZUMAB;IRINOTECAN
BEVACIZUMAB;LOMUSTINE
BEVACIZUMAB;OSIMERTINIB

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BEVACIZUMAB;PACLITAXEL
BEVACIZUMAB;PACLITAXEL ALBUMIN
BEVACIZUMAB;PACLITAXEL;TOPOTECAN
BEVACIZUMAB;PEMETREXED
BEVACIZUMAB;PEMETREXED DISODIUM
BEVACIZUMAB;TOPOTECAN
BEVACIZUMAB;TOPOTECAN HYDROCHLORIDE
BI 836880
BORTEZOMIB;SORAFENIB
BRIVANIB
BRIVANIB ALANINATE
BROLUCIZUMAB
BROLUCIZUMAB DBLL
CABOZANTINIB
CABOZANTINIB S-MALATE
CEDIRANIB
CEDIRANIB MALEAT
CHIAURANIB
CONBERCEPT
DOCETAXEL;RAMUCIRUMAB
DOVITINIB
DOVITINIB LACTATE
ENZASTAURIN
ENZASTAURIN DIHYDROCHLORIDE
ENZASTAURIN MONOHYDROCHLORIDE

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FLUOROURACIL;FOLIC ACID;OXALIPLATIN;ROGARATINIB
FORETINIB
FRUQUINTINIB
GOLVATINIB
GOLVATINIB TARTRATE
ICRUCUMAB
ILORASERTIB
IMATINIB MESILATE;VATALANIB
IMATINIB;VATALANIB
LENVATINIB
LENVATINIB MESILATE
LINIFANIB
LUCITANIB
MIDOSTAURIN
MOTESANIB
MOTESANIB DIPHOSPHATE
MUPARFOSTAT
NAVICIXIZUMAB
NINTEDANIB
NINTEDANIB ESILATE
OGLUFANIDE
OGLUFANIDE DISODIUM
ORANTINIB
PACLITAXEL;RAMUCIRUMAB
PAZOPANIB

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PAZOPANIB HYDROCHLORIDE
PEGAPTANIB
PEGAPTANIB SODIUM
PEGDINETANIB
PLITIDEPSIN
PONATINIB
PONATINIB HYDROCHLORIDE
PUQUITINIB
PUQUITINIB MESILATE
RAMUCIRUMAB
RANIBIZUMAB
RANIBIZUMAB;VERTEPORFIN
REGORAFENIB
ROGARATINIB
SEMAXANIB
SORAFENIB
SORAFENIB TOSILATE
SULFATINIB
SUNITINIB
SUNITINIB MALATE
SURAMIN
SURAMIN SODIUM
TESEVATINIB
TESEVATINIB TOSILATE
TIVOZANIB

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TIVOZANIB HYDROCHLORIDE
TIVOZANIB HYDROCHLORIDE MONOHYDRATE
VANDETANIB
VARISACUMAB
VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS
VATALANIB
VATALANIB SUCCINATE
VOROLANIB

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12 APPENDIX 2: ASSESSMENTS CUT OFF FOR INTERIM ANALYSIS

The following assessments with data recorded in the database after the completion of Cycle 8 will not be included for interim analysis in summary tables, figures, and listings.

Table 13: Assessments Excluded for Interim Analysis After Completion of Cycle 8

Assessment	Comment
RECIST assessments (Investigator/site and Central Imaging)	Timepoints beyond Cycle 8 Day 28 are excluded from interim analysis (e.g. Cycle 10 Day 28, etc.)
CHOI imaging assessment (Central Imaging)	Timepoints beyond Cycle 8 Day 28 are excluded from interim analysis (e.g. Cycle 10 Day 28, etc.)
Safety assessments presented in by-visit summary tables and listings (laboratory assessments, vital signs, electrocardiogram)	Timepoints beyond Cycle 8 Day 28 are excluded (e.g. Cycle 9 Day 1, etc.)
Rivoceranib dosing and drug accountability information	Timepoints beyond Cycle 8 Day 28 are excluded from interim analysis (e.g. Cycle 9 Day 1, etc.)

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13 APPENDIX 3: ADVERSE EVENTS OF SPECIAL INTEREST

Table 14: Final Rivoceranib AESI (PT's and MedDRA SMQ's)

Category	SMQ	Select PT
Hypertension	SMQ: hypertension (narrow)	
Proteinuria	SMQ: proteinuria (narrow)	
Dermatologic Toxicity		PT: palmar-plantar erythrodysaesthesia syndrome
	SMQ: severe cutaneous adverse reactions (narrow)	
Haemorrhage	SMQ: haemorrhage terms (excluding laboratory terms)	
Hepatotoxicity	SMQ: cholestasis and jaundice of hepatic origin	
		PT: hepatic Failure PT: hepatobiliary disease PT: liver disorder
QTc prolongation	SMQ: torsade de pointes/QT prolongation (narrow)	
Gastrointestinal perforation	SMQ: gastrointestinal perforation	
Renal impairment	SMQ; acute renal failure	
Thromboembolic events	SMQ: embolic and thrombotic events arterial SMQ: embolic and thrombotic events venous	
Posterior reversible encephalopathy syndrome		PT: posterior reversible encephalopathy syndrome

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Wound Healing impaired		PT: impaired healing, incisional hernia, incisional site impaired healing, postoperative wound complication
Pancreatitis	SMQ: acute pancreatitis	

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