NCT #: NCT04119453

CLINICAL PROTOCOL

Protocol No.: RM-202

Protocol Title: 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 No.: RM-202

Study Drug: Rivoceranib

Sponsor Medical Monitor: [redacted]
Elevar Therapeutics, Inc.
2825 E Cottonwood Pkwy, Suite 180
Salt Lake City, UT 84121
USA
Phone: [redacted]
Email: [redacted]

Sponsor Name: Elevar Therapeutics, Inc.
2825 E Cottonwood Pkwy, Suite 180
Salt Lake City, UT 84121
USA
Phone: (801) 303-7440

IND: 143,473

Approval Date: 11 June 2019
Amendment 1: 05 July 2019
Amendment 2: 09 January 2020
Amendment 3: 15 July 2020
Amendment 4: 22 October 2020

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

The information in this document is Elevar Therapeutics Inc's confidential information. This material may be used only for evaluating or conducting clinical investigations; any other proposed use requires written consent from Elevar Therapeutics, Inc. Acceptance of this document constitutes an agreement by the recipient(s) that no unpublished information contained herein will be published or disclosed without first obtaining written approval from Elevar Therapeutics, Inc. This document may be disclosed to appropriate Investigational Review Boards/Ethics Committee under the condition of confidentiality.

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SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Monitor

PROTOCOL TITLE: 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 NO: RM-202

PROTOCOL DATE: 11 June 2019
AMENDMENT 1: 05 July 2019
AMENDMENT 2: 09 January 2020
AMENDMENT 3: 15 July 2020
AMENDMENT 4: 22 October 2020

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

[redacted] [redacted] Date (YYYY-MM-DD)

Sponsor Medical Monitor

Elevar Therapeutics, Inc.

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: 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 NO: RM-202

PROTOCOL DATE: 11 June 2019
AMENDMENT 1: 05 July 2019
AMENDMENT 2: 09 January 2020
AMENDMENT 3: 15 July 2020
AMENDMENT 4: 22 October 2020

This protocol is a confidential communication of Elevar Therapeutics, Inc. I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also conduct the study consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Furthermore, I understand that the Sponsor, Elevar Therapeutics, Inc. and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Elevar Therapeutics, Inc.

I have read this protocol in its entirety and agree to conduct the study accordingly:

_____ _____

Principle Investigator's Signature Date (YYYY-MM-DD)

_____

Printed Name

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACC	adenoid cystic carcinoma
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BUN	blood urea nitrogen
CAP	cyclophosphamide, doxorubicin, cisplatin
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	clearance
Cmax	maximum observed serum concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DCR	disease control rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EGFR	epidermal growth factor receptor
FACT	functional assessment of cancer therapy
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Hb	hemoglobin
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HIPPA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PDGFR	platelet-derived growth factor receptor
PFS	progression free survival
PK	pharmacokinetic
PO	oral (per os)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
PVDC	polyvinylidene chloride
QD	once daily
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors
RR	risk ratio
SAE	serious adverse event
SD	stable disease
SoA	Schedule of Assessments
SUSAR	suspected unexpected serious adverse reaction
t1/2	terminal elimination half-life
T3	triiodothyronine
T4	thyroxine
TIA	transient ischemic attack
Tmax	time of peak concentration
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor

Abbreviation	Definition
VEGFR	vascular endothelial growth factor receptors
VEGFR-2	vascular endothelial growth factor receptor-2
WBC	white blood cell
WOCBP	women of child-bearing potential

PROTOCOL AMENDMENT 4.0 SUMMARY OF CHANGES

Study Title: 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

Summary of Changes:

Elevar Therapeutics, Inc. updated the RM-202 Protocol Amendment 3.0 (15 July 2020) to Amendment 4.0 (22 October 2020). The main purpose of this amendment is to add assessment of response by independent central review in addition to investigator/institutional assessment, add assessment by CHOI criteria in addition to RECIST, allow for subject replacement, and allow for possible preplanned interim analysis. **Bold** indicates added text, ~~strikethrough~~ indicates deleted text.

Key changes made from Protocol Amendment 3.0 to Amendment 4.0 are summarized by protocol section in the table below.

Minor editorial and formatting changes have also been made to enhance clarity and readability.

Section	Key Changes	Rationale for the Change
Synopsis and Section 3 Objectives and Endpoints, Primary Endpoints and Section 8.3.1 Efficacy Analyses, Analysis of the Primary Efficacy Endpoint	• Added ORR assessment using RECIST Version 1.1 to be performed by Investigator or Institutional assessment. • Added ORR assessment using RECIST Version 1.1 to be evaluated by Independent Central Review.	• To clarify the review will be performed by investigator/ institutional assessment • To add assessment by Independent Central Review
Synopsis and Section 3 Objectives and Endpoints, Secondary Endpoints and Section 8.3.1 Efficacy Analyses, Analysis of the Secondary Efficacy Endpoint	• Added that PFS, DoR, and TTP will be performed by Investigator or Institutional assessment using RECIST Version 1.1. • Added that PFS, DoR, and TTP will be performed by Independent Central Review using RECIST Version 1.1. • ORR and DoR (not DCR) will be summarized with frequencies and percentages	• To clarify the review will be performed by investigator/ institutional assessment • To add assessment by Independent Central Review

		• To clarify how ORR and DoR will be reported
Synopsis and Section 3 Objectives and Endpoints, Exploratory Endpoints and Section 8.3.3 Exploratory Analyses	• Added ORR assessment by Independent Central Review based on CHOI criteria. • Added that DCR will be performed by Investigator or Institutional assessment using RECIST Version 1.1. • Added that DCR will be performed by Independent Central Review using RECIST Version 1.1. • DCR will be summarized with frequencies and percentages. ORR will be evaluated using CHOI criteria.	• To add assessment based on CHOI criteria by Independent Central Review • To clarify the review will be performed by investigator/institutional assessment • To add assessment by Independent Central Review • To clarify how DCR and ORR will be reported
Synopsis and Section 8.3.1 Interim Analysis	Added that interim analysis may be performed after approximately 48 subjects either discontinue the study treatment or complete C8D28 tumor assessments (around week 32).	To allow for possible preplanned interim analysis
Synopsis and Section 4.3.4 End of Treatment or Discontinuation Visit	Subjects who discontinue treatment prematurely for reasons other than toxicity and disease progression may be replaced. Subjects who are deemed unevaluable due to lack of appropriate baseline or follow-up scans may also be replaced.	To allow for subject replacement
Section 7.1.1.1 RECIST Version 1.1	Added title to section. Added that efficacy assessment will also be performed by Independent Central Review as per the Imaging Charter.	To add assessment by Independent Central Review
Section 9 References, and Appendix 10 Tumor Response Criteria	• Added reference for CHOI criteria. • Added appendix 10 for tumor response criteria comparing RECIST 1.1 to CHOI criteria	To add tumor assessment by CHOI criteria
Section 7.4.5 Objective Response Rate (ORR)	Added new section for ORR as an exploratory assessment evaluated by Independent Central Review using CHOI criteria. The scans assessed using RECIST criteria will also be assessed using CHOI criteria by Independent Central Review per Imaging Charter. Freehand measurement of tumor is preferred but circular is permitted.	To add assessment using CHOI criteria by Independent Central Review
Section 8.2.3 Exploratory Population	• Edited the PK analysis population includes all subjects who have valid plasma concentrations.	To clarify which subjects are included in the PK analysis population and the

	• Added CHOI criteria population includes all subjects who have been treated with at least one dose of rivoceranib and have at least 1 post-baseline tumor assessment.	CHOI criteria population.
Section 8.3.1 Efficacy Analysis; Analysis of the Primary Efficacy Endpoint(s) Analysis of Secondary Efficacy Endpoint(s)	• Added that ORR will be evaluated using RECIST Version 1.1 separately by investigator/ institutional assessment and Independent Central Review. • Added that PFS will be evaluated separately by investigator/ institutional assessment and Independent Central Review. • Added that DoR will be evaluated separately by investigator/ institutional assessment and Independent Central Review. • Added that TTP will be evaluated separately by investigator/ institutional assessment and Independent Central Review.	To add ORR assessment by investigator/ institutional assessment and Independent Central Review To add PFS assessment by investigator/ institutional assessment and Independent Central Review To add DoR assessment by investigator/ institutional assessment and Independent Central Review To add TTP assessment by investigator/ institutional assessment and Independent Central Review
Section 8.3.2.2 Adverse Events	Added definition of TEAEs.	To clarify definition.
Section 8.3.3 Exploratory Analyses	• Added that DCR will be evaluated separately by investigator/ institutional assessment and Independent Central Review. • Added definition of ORR subjects. Added that ORR will be evaluated using CHOI criteria by Independent Central Review.	To add DCR assessments by investigator/ institutional assessment and Independent Central Review To add definition of ORR subjects. To add ORR assessments will be evaluated using CHOI criteria by Independent Central Review. ORR will be summarized.

1. PROTOCOL SUMMARY

1.1. Synopsis

<table>
<tr><td>Study Title</td><td colspan="2">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</td></tr>
<tr><td>Indication</td><td colspan="2">Recurrent or metastatic adenoid cystic carcinoma (ACC) of all sites</td></tr>
<tr><td>Sites</td><td colspan="2">Approximately 12 sites</td></tr>
<tr><td>Phase of Development</td><td colspan="2">Phase 2</td></tr>
<tr><td>Investigational Product</td><td colspan="2">Rivoceranib will be supplied as 100 mg and 200 mg film-coated tablets for oral (PO) administration</td></tr>
<tr><td rowspan="4">Objectives and Endpoints</td><td>Primary Objectives:</td><td>Primary Endpoints:</td></tr>
<tr><td>To evaluate the efficacy of rivoceranib in subjects with recurrent or metastatic ACC based on assessment of objective response rate (ORR).</td><td>• 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 Independent Central Review</td></tr>
<tr><td>Secondary Objectives:</td><td>Secondary Endpoints:</td></tr>
<tr><td>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)</td><td>Efficacy assessed by:
• OS at 1 year and 2 years
• PFS at 6 months, 12 months and 2 years per RECIST Version 1.1 by Investigator or Institutional assessment
• PFS at 6 months, 12 months and 2 years per RECIST Version 1.1 evaluated by Independent Central Review
• DoR per RECIST Version 1.1 by Investigator or Institutional assessment
• DoR per RECIST Version 1.1 evaluated by Independent Central Review
• TTP per RECIST Version 1.1 by Investigator or Institutional assessment
• TTP per RECIST Version 1.1 evaluated by Independent Central Review</td></tr>
</table>

	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:**
	• Objective response rate (ORR) • To evaluate Disease control rate (DCR) of rivoceranib in subjects with recurrent or metastatic ACC	• ORR evaluated by Independent Central Review based on the CHOI criteria. (freehand measurement of tumor is preferred but circular is permitted) • DCR per RECIST Version 1.1 by Investigator or Institutional assessment • DCR per RECIST Version 1.1 by 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 (t1/2)
	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 (Facit.org)
Study Design	This is a Phase 2, multicenter, open-label, single-arm study of rivoceranib to evaluate its efficacy and safety in adult subjects with metastatic ACC of all anatomic sites of origin. Subjects will be treated with oral rivoceranib, 700 mg daily during 28-day cycles. Subjects will be monitored for clinical and/or radiographic evidence of disease progression as assessed by tumor growth or the discovery of additional tumors. Restaging scans will be performed approximately every 8 weeks for the first year and then approximately every 12 weeks and at End of Treatment (EOT), or as clinically indicated. 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 approximately every 12 weeks thereafter (or with the standard of care restaging frequency for their disease) until initiation of a new therapy.	
Dose Modification Scheme	AEs will be evaluated according to criteria outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Individual subject treatments may be modified or interrupted based on observed hematologic and nonhematologic toxicities when the Investigator judges the toxicities to be at least possibly related to rivoceranib treatment. Modifications may be performed based on the grade of toxicity as outlined in **Table 1.**	

Table 1: Rivoceranib Treatment-related Adverse Event Management

* Use specific separate management guidelines for rivoceranib-related AEs of hypertension, proteinuria, oral mucositis, palmar-plantar erythrodysesthesia (hand-foot syndrome), and rivoceranib-class effect AEs of gastrointestinal perforation, and ejection fraction decrease as a measure of congestive heart failure (Appendix 8).

- Rivoceranib dose interruption up to 21 days is allowed for adverse events to improve or resolve.
- *Investigators should ultimately manage dose modification for individual subjects based on clinical judgement and are encouraged to discuss cases that are not clear with the Medical Monitor.*

Grade of Adverse Event (NCI CTCAE Version 5.0)	**Management**	**Follow-Up**
Grade 1[a]	• Use local practice to manage the AE[b] • Continue treatment without dose adjustment	**If persistent:** • Treat as Grade 2
Grade 2[a]	• Use local practice to manage the AE[b] • Rivoceranib may be pre-emptively dose reduced by one level at any time during the current cycle or in the next cycle	**If persists for >4 weeks or worsens:** • Contact Medical Monitor **Nonhematologic AE:** **If improves to ≤ Grade 1 within 4 weeks:** • Resume rivoceranib at the dose before reduction or at the pre-emptively reduced dose. **Hematologic AE:** **If improves to ≤ Grade 1 or baseline within 4 weeks:** • Resume rivoceranib at the dose before reduction or continue at the pre-emptively reduced dose
Grade 3-4[a]	• Use local practice to manage the AE[b] • Temporarily withhold rivoceranib	**If persists for >3 weeks:** • Contact Medical Monitor **Nonhematologic AE:** **If improves to ≤ Grade 1 or manageable Grade 2**

			within 3 weeks: • Resume rivoceranib at dose reduced by one level **Hematologic AE:** **If improves to ≤ Grade 1 or baseline within 3 weeks:** • Resume rivoceranib at dose reduced by one level

[a.] Refer to NCI-CTCAE Version 5.0 for term-specific grading criteria.

[b.] Contraindicated concomitant medications should not be given unless benefit outweighs the risk per the Investigator's judgement.

Dose reduction should be limited to once every administration cycle (28 days/cycle) and reductions are permitted as outlined in Table 2 unless discussed and agreed upon between the Investigator and the Medical Monitor. A total of three dose reductions are permitted; however, dose reductions below 200 mg once daily (QD) will not be permitted. Additional dose reductions based on Investigator's clinical judgement are permitted if discussed and agreed upon with the Medical Monitor.

A dose reduction skipping one dose level down to the next level is permitted if discussed and agreed upon with the Medical Monitor.

If dose is reduced down by skipping one dose level, the dose can be resumed at one immediate level up (skipped level) based on patient's tolerance and Investigator's clinical judgement and upon discussion with the Medical Monitor.

Table 2: Recommended Dose Modification Levels for Management of Rivoceranib Toxicity

Starting Dose	**700 mg QD**
Dose Level -1	**500 mg QD**
Dose Level -2	**300 mg QD**
Dose Level -3	**200 mg QD**

Inclusion Criteria	Subjects are eligible to be included in the study only if all the following criteria apply: *Disease Related* 1. Histologically or cytologically confirmed metastatic/recurrent ACC not amenable to potentially curative surgery or radiotherapy 2. Evidence of disease progression by RECIST v1.1 Note: Disease progression is defined as one of the following occurring within the 6 months prior to study entry: a. At least a 20% increase in radiologically or clinically measurable lesions b. Appearance of any new lesions

3. Presence of at least one measurable target lesion which is evaluable by RECIST v1.1 criteria
4. Patients are eligible if CNS metastases have been treated and patients are neurologically returned to baseline or neurologically stable in the opinion of Investigator (except for residual signs or symptoms related to the CNS treatment) for at least 4 weeks prior to first dose of study drug administration. In addition, patients must be either off corticosteroids, or on a stable dose or decreasing dose of <20 mg daily prednisone or prednisone equivalent.

   Note: Only subjects with a known history or indication of CNS disease are required to have CNS imaging prior to study entry

Laboratory

5. Adequate organ and marrow function within 14 days prior to the first dose of rivoceranib administration, defined as:
   a. Absolute neutrophil count ≥1500/μL
   b. Platelet count ≥100,000/μL
   c. Serum bilirubin ≤1.5× upper limit of normal (ULN)
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0×ULN (≤5.0×ULN, if with liver metastasis)
   e. Estimated Creatinine Clearance >50 mL/min (Cockcroft-Gault)
   f. Partial thromboplastin time (PTT), prothrombin time (PT) and international normalized ratio (INR) ≤1.5×ULN
   g. Hemoglobin ≥9.0 g/dL
6. Urinary protein <2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine or urine protein/creatinine ratio must be collected and must demonstrate <2 g of protein in 24 hours

Demographic

7. Men and women ≥18 years of age (or age of majority, if higher per local regulations)
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Ethical/Other

9. The ability to understand and the willingness to sign a written informed consent
10. Female subjects who are of non-reproductive potential (i.e., post-menopausal by history – no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test within 72 hours prior to the first dose of rivoceranib
11. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices, complete abstinence, or sterilized partner) and a barrier method (e.g., condoms, cervical ring, sponge, etc.) during the period of therapy and for 30 days after the final dose of rivoceranib. Female subjects should also refrain from breastfeeding and egg donation and males should refrain from sperm donation throughout this period
12. QTc interval <480 milliseconds (ms) (CTCAE Grade 1) using Fredericia's QT correction formula

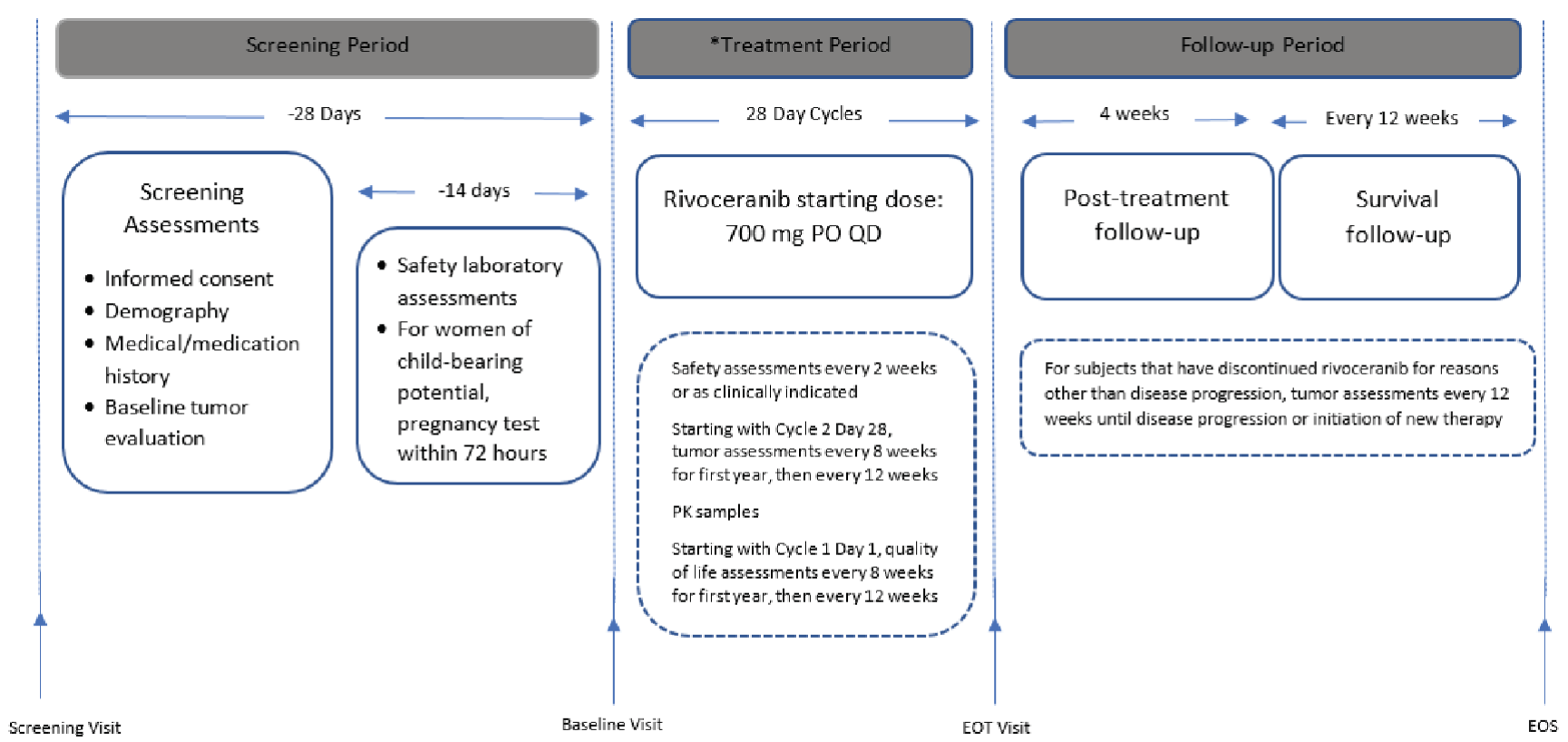
Exclusion Criteria	Subjects will be excluded from the study if any of the following criteria apply: *Disease Related* 1. Previous treatment with rivoceranib 2. Known hypersensitivity to rivoceranib or components of the formulation 3. Packed red blood cell transfusion or erythropoietin therapy within 14 days prior to the first dose of rivoceranib administration 4. History of another malignancy within 3 years prior to enrollment. A subject with the following malignancies is eligible for this study if, surgically and medically treated and in the opinion of the Investigator, they do not pose a significant risk to life expectancy or not likely to recur within 3 years: a. Carcinoma of the skin without melanomatous features b. Curatively treated cervical carcinoma in situ c. Bladder tumors considered superficial such as noninvasive (T1a) and carcinoma in situ (Tis) d. Thyroid papillary cancer with prior treatment e. Prostate cancer which has been surgically or medically treated 5. Prior chemotherapy, radiation therapy or major surgery within 4 weeksprior to rivoceranib administration or presence of any nonhealing wound (procedures such as catheter placement are not considered to be major surgery). Prior immunotherapy within 12 weeks prior to first dose of study drug. Palliative radiotherapy to non-target lesions within 2 weeks prior to rivoceranib administration or biopsy any time prior to rivoceranib administration is permitted 6. Prior tyrosine kinase inhibitor therapy targeting vascular endothelial growth factor receptors (VEGFR), within 5 half-lives prior to rivoceranib administration 7. Subjects who have not recovered to ≤ Grade 1 from prior tyrosine kinase inhibitor-related adverse events 8. History of uncontrolled hypertension based on Investigator's clinical judgement (consistent blood pressure readings ≥140/90 mmHg and/or change in antihypertensive medication within 7 days prior to rivoceranib administration) 9. History of severe adverse events including uncontrolled hypertension or other common anti-angiogenesis class drug effects (e.g., ramucirumab) that may indicate a higher risk to the safety of the subject if provided further anti- angiogenesis treatment, in the Investigator's opinion 10. History of vascular disease including arterial or venous embolic events (pulmonary embolism), other than hypertension, within the last 3 months prior to treatment with rivoceranib (e.g., hypertensive crisis, hypertensive encephalopathy, stroke or transient ischemic attack [TIA], or significant peripheral vascular diseases) that, in the Investigator's opinion, may pose a risk to the subject on vascular endothelial growth factor (VEGF) inhibitor therapy 11. History of bleeding diathesis or clinically significant bleeding within 14 days prior to treatment with rivoceranib 12. History of clinically significant thrombosis within 3 months prior to treatment with rivoceranib that, in the Investigator's opinion, may place the subject at risk of side effects from anti-angiogenesis products

	13. Therapy with systemic anticoagulant or antithrombotic agents within 7 days prior to treatment with rivoceranib that in the Investigator's opinion could interfere with clotting. The maximum allowable daily dose of aspirin is 325 mg 14. Gastrointestinal malabsorption, or any other condition that in the opinion of the Investigator might affect the absorption of rivoceranib 15. History of clinically significant glomerulonephritis, biopsy-proven tubulointerstitial nephritis, crystal nephropathy, or other renal insufficiencies 16. An uncontrolled intercurrent illness including, but not limited to any of the following: a. Ongoing or active infection (including minor localized infections) requiring oral or intravenous treatment b. Symptomatic class 3 or 4 congestive heart failure, defined as a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood c. Unstable angina pectoris d. Cardiac arrhythmia e. Any other illness or condition that the treating Investigator feels would interfere with study compliance or would compromise the subject's safety or study endpoints *Ethical/Other* 17. A female subject who is pregnant or breast-feeding 18. Psychiatric illness/social situations that would limit compliance with study requirements 19. History of drug or alcohol abuse within the past 5 years 20. Known seropositive requiring anti-viral therapy for human immunodeficiency virus (HIV) infection 21. Known seropositive requiring antiviral therapy for hepatitis B virus (HBV) infection OR evidence of active hepatitis B infection by detectable viral load if the antibody tests are positive NOTE: A positive hepatitis B core antibody (HBcAb) subject with an undetectable surface antigen and negative hepatitis B DNA test (e.g., polymerase chain reaction [PCR] test) can be enrolled 22. Known seropositive requiring antiviral therapy for hepatitis C virus (HCV) infection OR subjects with positive hepatitis C virus antibody NOTE: A positive Anti-HCV subject with an undetectable/negative hepatitis C RNA test can be enrolled 23. Participation in another clinical study with any investigational medication or product administered within ≤28 days prior to first dose of rivoceranib 24. Subjects unable or unwilling to discontinue excluded medications for at least 5 half-lives prior to first dose of study drug

Concomitant Therapy	Excluded Therapy • Other anticancer therapy, systemic chemotherapy, radiotherapy (radiation as a palliative therapy to treat bone metastasis will be allowed), immunotherapy, cancer-related hormone therapy (cancer unrelated alternative hormone therapy that was initiated prior to the study enrollment is allowed) or herbal medicines that have official indication as anticancer drugs, or administration of investigational agents from other clinical studies • Medications known or suspected to prolong the QT/QTc interval, except for drugs with low risk of QT/QTc prolongation • All herbal supplements (including St John's wort), food and drinks that contain grapefruit, Seville oranges or orange marmalade • Strong inducers or inhibitors of CYP3A4 and CYP2D6 should be avoided. In case a prohibited medication without a safer alternative is mandatory to treat an AE and it would make it unsafe to continue rivoceranib, the subject will be withdrawn from rivoceranib. Allowed Therapy Medications for treatment of underlying non-cancer disease and symptomatic treatment of AEs are permitted. Packed red blood cell transfusion or erythropoietin therapy can be used after the initiation of the treatment at the Investigator's discretion; use must be recorded in the electronic case report form (eCRF). Prophylactic use of anti-diarrheal and anti-nausea medications that are not excluded are permitted at the Investigator's discretion. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor, if required.
Population	Subjects with ACC of all anatomic sites of origin who have had disease progression within the last 6 months, and who are not amenable to potentially curative surgery or radiotherapy.
Duration of Treatment	All subjects may remain on treatment until occurrence of disease progression, unacceptable toxicity, death, the withdrawal of consent from treatment, lost to follow-up or study termination by the Sponsor. When a subject discontinues rivoceranib for any reason, the subject will enter the 24-month survival follow-up period until withdrawal of consent from the study, lost to follow-up, end of the study or death, whichever occurs earlier.
Duration of Study	The maximum duration of the study is estimated to be 48 months and includes screening, treatment and follow-up phases.
Number of Subjects	Approximately 72 subjects
Replacement of Subjects	Subjects who discontinue treatment prematurely for reasons other than toxicity and/or disease progression may be replaced. Subjects who are deemed unevaluable due to lack of appropriate baseline or follow-up scans may also be replaced.
Statistical Methods	Data collected in this study will be presented descriptively using summary tables, figures and data listings. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.

	Efficacy Analyses The primary efficacy endpoint is the ORR defined as the proportion of subjects who achieve confirmed complete response (CR) or partial response (PR) per RECIST Version 1.1. The ORR and DoR will be summarized with frequencies and percentages. A 95% confidence interval (CI) will be constructed for the ORR and DCR using an exact binomial method. The OS, PFS, and TTP will be estimated using the Kaplan-Meier method. **Safety Analyses** Safety data will be summarized and listed by subject. Summary tables will show incidence rates (number of subjects with at least one event) of AEs and serious adverse events (SAEs), as well as summaries of severity (CTCAE Version 5.0). Shift tables will be presented for parameters of interest.
	Exploratory Analyses Correlative biomarker analyses in tumor tissues will be performed. A separate statistical analysis plan (if performed) will outline details of the biomarker and PK analyses. Patient reported outcomes will be assessed using the FACT-G questionnaire. The scores from these questionnaires will be summarized by study visit using descriptive statistics. DCR (CR+PR+stable disease) will be summarized with frequencies and percentages. ORR will be evaluated using CHOI criteria.
Sample Size Determination	The sample size of 72 subjects is based on 10% dropout rate, 90% power at a two-sided 5% significance level with the target ORR at 25% to identify difference from the historical rate of 10%. With a sample size of 72 subjects, the lower bound of the 95% CI will be greater than 10% with the target ORR at 25%.
Interim Analysis	Interim analysis may be performed after approximately 48 subjects either discontinue the study treatment or complete C8D28 tumor assessments (around week 32)

1.2. Study Schema



Abbreviations: EOS=end of study; EOT=end of treatment; PK=pharmacokinetic; PO=oral; QD=once daily

Note: Eligibility will be confirmed before the subject receives the first dose of rivoceranib
*Cycles may continue until progression of disease, discontinuation or end of treatment

1.3. Schedule of Assessments (SoA)

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	
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.

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**	
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.

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	
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.

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.

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**	
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

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**	
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.

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.

[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.

2. INTRODUCTION

Rivoceranib (also known as apatinib and YN968D1) is an orally administered small molecule, selective vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor that is being developed as a therapeutic option for patients with recurrent or metastatic adenoid cystic carcinoma (ACC) of all anatomic sites of origin.

2.1. Study Rationale

Vascular endothelial growth factor (VEGF) overexpression has been associated with poor outcomes in ACC (Zhang, 2005). Sorafenib, a small molecule inhibitor of vascular endothelial growth factor receptor (VEGFR), has shown modest activity in recurrent and metastatic ACC of the salivary gland (Locati, 2016). Two studies examined efficacy of lenvatinib, a multi-tyrosine kinase inhibitor, which inhibits VEGFR, as well as fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR). Lenvatinib showed promising activity in a small number of subjects with recurrent and metastatic ACC, including cancers arising from non-salivary gland primary sites with overall response rates of 16% (Tchekmedyian, 2018). Lenvatinib showed an overall response rate of 11% in 28 subjects with ACC of the salivary glands (Locati, 2018). Axitinib showed a partial response (PR) of 9% in 33 subjects with recurrent/metastatic ACC (Ho, 2016).

Rivoceranib, a selective VEGFR-2 inhibitor, has been approved for the indication of gastric cancer (GC) in China since 2014 based on a Phase 3 study in patients with chemotherapy-refractory or metastatic adenocarcinoma of the stomach or gastroesophageal junction (Li, 2016; Scott, 2018), and is being evaluated globally in a randomized Phase 3 trial for GC (NCT03042611). In addition, results of a Phase 2 study evaluating rivoceranib in 59 subjects in China with recurrent or metastatic ACC showed an ORR and disease control rate (DCR) of 47.1% and 98.1%, respectively (Zhu, 2018).

Rivoceranib has received orphan drug designation for GC by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

This Phase 2 study is designed to demonstrate the efficacy and safety of rivoceranib in adult subjects with recurrent or metastatic ACC of all anatomic sites of origin. In addition, pharmacodynamic activity of rivoceranib will be evaluated as well as the subject's quality of life. The results from this study will help guide treatment for this population of patients, who currently have limited treatment options.

2.2. Background

2.2.1. Adenoid Cystic Carcinoma

ACC is a relatively uncommon tumor with a reported incidence of 4.5 cases per million individuals (Moskaluk, 2013). ACC is the second most common malignancy of salivary glands (Wysocki, 2016), and is characterized by slow growth and perineural invasion (Dillon, 2016). ACC may also occur in secretory glands located in other tissues, such as in the tracheobronchial tree, esophagus, breast, lungs, prostate, uterine cervix, and vulva (Dillon, 2016).

ACC is considered a low-grade malignancy (Chae, 2015). Although good local control is usually achieved by resection of the primary tumor and adjuvant radiation therapy, more than half of patients eventually have recurrent and/or metastatic disease (Wysocki, 2016). Short-term prognosis is favorable with an expected 5-year survival rate of 77%; however, rates drop significantly after 10 and 15 years with survival estimated at 60% and 45% respectively (Wysocki, 2016). Most patients die as a result of disease progression (Wysocki, 2016).

ACC consists of two different cell types: inner luminal epithelial cells and outer myoepithelial cells. Each cell line tends to express different molecular biomarkers; epithelial cells express c-kit, cox-2 and Bcl-2, while myoepithelial cells express epidermal growth factor receptor (EGFR) and *MYB* (Chae, 2015). The molecular pathogenesis of ACC has not been well described. Specific translocations of a transcription factor, *MYB* or *MYB-L1*, have been characterized and thought to be a key carcinogenic event for ACC, but its biology and downstream targets have not yet been elucidated (Brayer, 2016).

Effective treatment to prevent indolent ACC from evolving into recurrent, metastatic disease remains a challenge (Chae, 2015). Given the high rate of late local recurrence and distant metastasis, ACC patients require intensive oncological surveillance. (Wysocki, 2016).

2.2.2. Current Management Options

There is no standard of care treatment option for ACC, and there is an unmet need for patients with recurrent and/or metastatic ACC.

Radical excision and postoperative radiation is mainly used for locoregional control of early stage disease (Chae, 2015).

There is no accepted standard systemic chemotherapy for patients with ACC tumors (Chae, 2015). Due to its slow growth, systemic chemotherapy has been reported to be suboptimal with low response rates (Dillon, 2016). The combination of cyclophosphamide, doxorubicin, and cisplatin (CAP) is frequently used based on a small Phase 2 study (Licitra, 1996)

Most clinical trials with small molecule inhibitors of tyrosine kinases targeting c-KIT (a known oncoprotein), PDGFR, and FGFR have shown poor response rates of less than 10% (Chae, 2015).

Phase 2 trials evaluating multi-targeted tyrosine kinase inhibitors, including sunitinib (Chau, 2012), sorafenib (Thomson, 2015), dovitinib (Dillon, 2017), and axitinib (Ho, 2016) have also demonstrated low rates of response and disease stabilization.

2.2.3. Angiogenesis Inhibitors

Unlike conventional chemotherapy, angiogenesis inhibitors primarily target neovascularization and/or survival of existing tumoral blood vessels. VEGF and VEGFRs are recognized as components of one of the main signaling pathways in angiogenesis (Lee, 2015). VEGF binds to VEGFR inducing a series of vascular angiogenesis reactions such as cell proliferation, migration, blood vessel permeability and migration of stem cells from bone marrow. Tumors cannot grow beyond 2 mm^3 without adequate oxygen and nutrients supplied via blood vessels (Wu, 2018); most human tumors produce a high level of VEGF to trigger production of vasculature necessary to sustain tumor growth.

The family members of VEGF receptors include: VEGFR-1 (Flt-I), VEGFR-2 (KDR/Flk-I), and VEGFR-3 (Flt-4). Vascular angiogenesis in tumors is mainly induced by VEGF binding to VEGFR-2 (KDR/Flk-l). VEGF/VEGFR-2 signaling in tumor vascular endothelial cells is recognized as a pivotal and rate-limiting step in tumor angiogenesis.

Various non-specific inhibitors which target the VEGFR family include sorafenib, vandetanib, cediranib, and sunitinib. Lack of specificity may contribute to the adverse events (AEs) associated with these agents; administration of sunitinib has been associated with left ventricular dysfunction, hemorrhagic events, hypertension, and abnormal adrenal function.

Despite significant side effects, inhibitors of VEGF and VEGFR play an important role in the management of cancer.

2.2.4. Rivoceranib

Rivoceranib has been shown to be a potent and selective inhibitor of VEGFR-2 (IC_{50} approximately 1 nM). Rivoceranib compared with other VEGF inhibitors shows significantly less inhibition of other key angiogenesis receptors such as Ret, VEGFR-l, PDGFR-β, c-kit, FGFR1, and VEGFR-3. This higher affinity may allow for more specific and effective inhibition of VEGFR-2, which would minimize side effects occurring from off-target inhibition.

Rivoceranib was evaluated in a single-arm Phase 2 study in 59 subjects with recurrent/metastatic ACC of the head and neck at a dose of 500 mg once daily (QD). The 6-month progression free survival (PFS) rate was 87.9% (95% confidence interval [CI], 76.6%–99.1%), and the 12-month PFS rate was 50.7% (95% CI 21.8%–79.7%). The 12-month overall survival (OS) rate was 96.3% (95% CI, 91.3%–101.3%). The ORR and DCR were 47.1% and 98.1%, respectively.

The incidence of drug-related AEs was 88.1% (52/59); 22.0% (13/59) of subjects developed AEs of ≥ Grade 3. The most common AEs were hypertension (54.2%), hand-foot syndrome (33.9%), and proteinuria (23.7%). A total of 34 (57.6%) subjects required dose reduction. This study demonstrated that rivoceranib appears to be effective and safe for recurrent/metastatic ACC of the head and neck (Zhu, 2018).

For the most comprehensive nonclinical and clinical information regarding rivoceranib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology, refer to the latest version of the rivoceranib Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

A meta-analysis, which included 7 randomized controlled studies comprising 800 subjects, examined the short-term efficacy and safety of rivoceranib or combination therapy for GC, hepatocellular carcinoma and non-small-cell lung cancer. The treatment of cancers using rivoceranib was more successful compared to therapy without rivoceranib. Both ORRs and DCRs were significantly improved in the rivoceranib group compared to those in the control group (risk ratio [RR]=2.18, 95% CI 1.30–3.65; RR=2.09, 95% CI 1.21–3.60) (Xue, 2018).

Based on the short-term acute adverse reactions of rivoceranib, significant differences between groups were found for hypertension, urine protein, hand-foot syndrome, and gastrointestinal reactions (diarrhea), while no significant differences were found for myelosuppression, nausea and vomiting. A retrospective cohort study showed that most of the adverse reactions occurred in the first cycle of the rivoceranib treatment.

The original studies included in the meta-analysis, reported that most adverse reactions were Grade 1 or Grade 2 and were controllable. Moreover, the results showed that rivoceranib prolonged survival (Hazard Ratio [HR]=0.38, 95% CI: 0.28–0.52), and the effect was more pronounced in subjects treated with 750 mg QD or 850 mg QD of rivoceranib than in those treated with a dose of ≤500 mg QD.

The study design aims to minimize potential risks to subjects participating in this study based on the protocol inclusion and exclusion criteria (Sections 5.1 and 5.2).

The risk-to-benefit ratio for subjects participating in this study is considered acceptable based upon limited treatment options for study subjects with recurrent or metastatic ACC.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of rivoceranib may be found in the latest version of the IB.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of rivoceranib in subjects with recurrent or metastatic adenoid cystic adenocarcinoma (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 RECIST Version 1.1 evaluated by Independent Central Review.
Secondary	
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)	Efficacy assessed by: • OS at 1 year and 2 years • PFS at 6 months, 12 months and 2 years per RECIST Version 1.1 by Investigator or Institutional assessment • PFS at 6 months, 12 months and 2 years per RECIST Version 1.1 evaluated by Independent Central Review • DoR per RECIST Version 1.1 by Investigator or Institutional assessment • DoR per RECIST Version 1.1 evaluated by Independent Central Review • TTP per RECIST Version 1.1 by Investigator or Institutional assessment • TTP per RECIST Version 1.1 evaluated by Independent Central Review
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	
Objective response rate (ORR) • To evaluate Disease control rate (DCR) of rivoceranib in subjects with recurrent or metastatic ACC	• ORR evaluated by Independent Central Review based on the CHOI criteria (freehand measurement of tumor is preferred but circular is permitted) • DCR per RECIST Version 1.1 by Investigator or Institutional assessment • DCR per RECIST Version 1.1 by 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 (Facit.org)

4. STUDY DESIGN

4.1. Overall 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 up to 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 (Section 6.5).

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 judgement. 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

Version 1.1. All scans should be available for submission to central archiving and 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.

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.

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

4.2. Justification for Dose

There is an unmet medical need for more effective therapies for subjects with recurrent or metastatic ACC.

The study design will employ a starting dose of 700 mg rivoceranib administered orally QD, which is similar to the maximum tolerated dose (MTD) determined by previous clinical studies conducted by Elevar Therapeutics, Inc.

A Phase 1/2a study evaluated five dose cohort levels of rivoceranib at 81, 201, 403, 604, and 685 mg (administered as 100, 250, 500, 750, and 850 mg rivoceranib mesylate, respectively).

The Phase 1 study escalated to 685 mg, which was selected as the recommended Phase 2 dose. In the Phase 2 portion, 30 subjects were enrolled at the 685-mg starting dose and over the course of two 28-day cycles only 4 subjects required dose reductions. Subjects from Phase 1 who started at lower doses required no dose reductions over the two 28-day cycles of the study (Sharma, 2015).

A global, pivotal Phase 3 study in advanced GC is ongoing and is using a starting dose of 700 mg rivoceranib (NCT03042611).

A Phase 1 dose escalation study conducted in China evaluated the same doses with the addition of an 805-mg cohort (1000 mg rivoceranib mesylate) and found the 805-mg dose to be intolerable, resulting in determination of the MTD as 685 mg (Li, 2010).

In summary, the results from previous clinical studies determined that the proposed starting dose for rivoceranib of 700 mg administered orally QD is similar to the MTD and should be tolerated by subjects with recurrent or metastatic ACC.

Dose modification should be performed if needed according to the schedule in Section 6.5.

4.3. Study Phases from Screening to End of Study

4.3.1. Screening

Any procedures or assessments associated with this study may only be performed after obtaining written informed consent from potential subjects. Upon signing the informed consent form, the screening period will start. Screening should be completed within 28 days before the date of initial administration of rivoceranib (Cycle 1 Day 1 or Baseline visit). Hematology, blood chemistry, coagulation and urinalysis should be completed within 14 days before the Baseline visit. Thyroid tests should be obtained 28 days before the Baseline visit. A pregnancy test should be completed within 72 hours before the Baseline visit in women of child-bearing potential (WOCBP). Serological tests should be performed within 2 years of study enrollment to satisfy eligibility criteria.

Screen failures (i.e., subjects who are consented but do not meet study eligibility criteria for participation in this study) may be rescreened (if clinically appropriate).

A master log of all consented subjects will be maintained at the site and will document all screen failures including the reason(s) for screen fail.

4.3.2. Enrollment

Subjects are eligible to be enrolled in the study if they meet all the inclusion and exclusion criteria. Protocol waivers or exemptions are not allowed. Eligibility will be confirmed before the subject receives the first dose of rivoceranib.

4.3.3. Treatment

Enrolled subjects will receive daily oral treatment with rivoceranib.

The study treatment will be continued until end of treatment (Section 4.3.4). Subjects are required to visit the investigational site at regular intervals according to the Schedule of Assessments (SoA) (Section 1.3). When a subject discontinues rivoceranib for any reason, the subject will enter the 24-month long-term follow-up period until withdrawal of consent, lost to follow-up, end of the study or death, whichever occurs earlier.

4.3.4. End of Treatment or Discontinuation Visit

Subjects who discontinue study treatment as defined below are required to complete the EOT visit within 7 days from their final administration of rivoceranib.

Subjects will not receive any further rivoceranib if any of the following occur:

- Withdrawal of consent from further treatment with rivoceranib
- Lost to follow-up
- Subject has an AE that in the opinion of the Investigator or the Sponsor warrants discontinuation of further dosing (APPENDIX 4)
- Subject intends to become pregnant
- Confirmation of disease progression and Investigator determination that the subject is no longer benefiting from treatment with rivoceranib
- Subject noncompliance that in the opinion of the Investigator or Sponsor warrants withdrawal, e.g., refusal to adhere to scheduled visits or assessments.
- Initiation of alternative anticancer therapy including another investigational agent

For subjects who discontinue from rivoceranib, the primary reason for early discontinuation from treatment should be documented on the appropriate eCRF.

Subjects who discontinue treatment prematurely for reasons other than toxicity and disease progression may be replaced. Subjects who are deemed unevaluable due to lack of appropriate baseline or follow-up scans may also be replaced.

4.3.5. Follow-up Phase

All subjects who permanently discontinue rivoceranib and do not initiate new anticancer therapy will be followed for AEs and SAEs through the Post-treatment Follow-up visit. In addition, if the subjects have discontinued for reasons other than progressive disease (PD) and met criteria otherwise (e.g., discontinued for AE and no new anticancer therapy), subjects will be followed with tumor assessments every 12 weeks (± 7 days) until PD or initiation of a new therapy.

All subjects will be followed for survival via telephone contact or other means (e.g., clinic visit) during the Long-term Follow-up.

4.3.5.1. Post-treatment Follow-up

For the purpose of safety follow-up, a Post-treatment Follow-up visit should be conducted at 28 days (± 7 days) after the EOT visit.

4.3.5.2. Long-term Follow-up

Subjects who permanently discontinue study treatment but who are not withdrawn from the study will continue follow-up at 12-week intervals (± 7 days) for tracking of their disease progression status (until PD or initiation of a new therapy, whichever occurs earlier) and survival status. 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 post-treatment

follow-up visits were not completed, the long-term follow-up will occur every 12 weeks from the last dose of study drug.

The survival follow-up can be performed via telephone, certified letter, or during subject's visit to the investigational site or other clinic site where confirmation of survival information documentation can be obtained. If the subject cannot be contacted successfully despite all attempts, including other contacts such as relatives, the subject will be considered lost to follow-up, and death information could be obtained through a public record search if local agencies permit.

4.3.6. End of Study

Premature discontinuation from the study (without EOT and any follow-up visits) will occur under the following circumstances:

- Subject withdrew consent for all study activities
- Investigator's discretion

- Lost to follow-up
  - Lost to follow-up should be recorded as such in the eCRF
  - The Investigator should show due diligence by documenting in the source documents steps taken to contact the subject
- Death
- Study termination by Sponsor
- Other, as per the discretion of the Sponsor or health authority

4.4. Stopping Criteria

The Sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies with rivoceranib indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Noncompliance that might significantly jeopardize the validity or integrity of the study
- Sponsor decision to terminate rivoceranib development

If the Sponsor determines that temporary suspension or termination of the study is required, the Sponsor will discuss the reasons for taking such action with all participating Investigators. When feasible, the Sponsor will provide advance notice to all participating Investigators of the impending action.

In order to fulfill a continued commitment to safety throughout the trial, all AEs will continue to be monitored in an ongoing fashion and the Medical Monitor may call an ad-hoc meeting with the lead Investigators at any time to determine if the study should continue. If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform all Investigators, and/or institutions conducting the study. The Sponsor will also promptly inform the relevant regulatory authorities of the suspension or termination decision along with the reasons for such action. Where required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason(s) for the suspension or termination. If the study is suspended for safety reasons and it is deemed appropriate by the Sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

5. STUDY POPULATION

5.1. Inclusion Criteria

Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

Disease Related

1. Histologically or cytologically confirmed metastatic/recurrent ACC not amenable to potentially curative surgery or radiotherapy
2. Evidence of disease progression by RECIST v1.1

Note: Disease progression is defined as one of the following occurring within the 6 months prior to study entry:

a. At least a 20% increase in radiologically or clinically measurable lesions
b. Appearance of any new lesions

3. Presence of at least one measurable target lesion which is evaluable by RECIST Version 1.1 criteria
4. Patients are eligible if CNS metastases have been treated and patients are neurologically returned to baseline or neurologically stable in the opinion of Investigator (except for residual signs or symptoms related to the CNS treatment) for at least 4 weeks prior to first dose of study drug administration. In addition, patients must be either off corticosteroids, or on a stable dose or decreasing dose of <20 mg daily prednisone or prednisone equivalent.

Note: Only subjects with a known history or indication of CNS disease are required to have CNS imaging prior to study entry

Laboratory

5. Adequate organ and marrow function within 14 days prior to the first dose of rivoceranib administration, defined as:
   a. Absolute neutrophil count ≥1500/μL
   b. Platelet count ≥100,000/μL
   c. Serum bilirubin ≤1.5×upper limit of normal (ULN)
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0×ULN (≤5.0×ULN, if with liver metastasis)
   e. Estimated Creatinine Clearance >50 mL/min (Cockcroft-Gault)
   f. Partial thromboplastin time (PTT), prothrombin time (PT) and international normalized ratio (INR) ≤1.5×ULN
   g. Hemoglobin ≥9.0 g/dL

6. Urinary protein <2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine or urine protein/creatinine ratio must be collected and must demonstrate <2 g of protein in 24 hours

Demographic

7. Men and women ≥18 years of age (or age of majority, if higher per local regulations)

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (APPENDIX 3)

Ethical/Other

9. The ability to understand and the willingness to sign a written informed consent

10. Female subjects who are of non-reproductive potential (i.e. post-menopausal by history – no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test within 72 hours prior to the first dose of rivoceranib (APPENDIX 5)

11. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (e.g. implants, injectables, combined oral contraceptives, some intrauterine devices, complete abstinence, or sterilized partner) and a barrier method (e.g. condoms, cervical ring, sponge, etc.) during the period of therapy and for 30 days after the final dose of rivoceranib. Female subjects should also refrain from breastfeeding and egg donation and males should refrain from sperm donation throughout this period (APPENDIX 5)

12. QTc interval <480 milliseconds (ms) (CTCAE Grade 1) using Fredericia's QT correction formula

5.2. Exclusion Criteria

Subjects will be excluded from the study if any of the following criteria apply:

Disease Related

1. Previous treatment with rivoceranib

2. Known hypersensitivity to rivoceranib or components of the formulation

3. Packed red blood cell transfusion or erythropoietin therapy within 14 days prior to the first dose of rivoceranib administration

4. History of another malignancy within 3 years prior to enrollment. A subject with the following malignancies is eligible for this study if surgically and medically treated and, in the opinion of the Investigator, they do not pose a significant risk to life expectancy or not likely to recur within 3 years:

a. Carcinoma of the skin without melanomatous features

b. Curatively treated cervical carcinoma in situ

c. Bladder tumors considered superficial such as noninvasive (T1a) and carcinoma *in situ*

(Tis)

d. Thyroid papillary cancer with prior treatment

e. Prostate cancer which has been surgically or medically treated

5. Prior chemotherapy, radiation therapy or major surgery within 4 weeks prior to rivoceranib administration or presence of any nonhealing wound (procedures such as catheter placement are not considered to be major surgery). Prior immunotherapy within 12 weeks prior to first dose of study drug. Palliative radiotherapy to non-target lesions within 2 weeks prior to rivoceranib administration or biopsy any time prior to rivoceranib administration is permitted

6. Prior tyrosine kinase inhibitor therapy targeting VEGFR, within 5 half-lives prior to rivoceranib administration

7. Subjects who have not recovered to ≤ Grade 1 from prior tyrosine kinase inhibitor-related adverse events

8. History of uncontrolled hypertension based on Investigator's clinical judgement (consistent blood pressure readings ≥140/90 mmHg and/or change in antihypertensive medication within 7 days prior to rivoceranib administration)

9. History of severe adverse events including uncontrolled hypertension or other common anti-angiogenesis class drug effects (e.g. ramucirumab) that may indicate a higher risk to the safety of the subject if provided further anti-angiogenesis treatment, in the Investigator's opinion

10. History of vascular disease including arterial or venous embolic events (pulmonary embolism), other than hypertension, within the last 3 months prior to treatment with rivoceranib (e.g. hypertensive crisis, hypertensive encephalopathy, stroke or transient ischemic attack [TIA], or significant peripheral vascular diseases) that, in the Investigator's opinion, may pose a risk to the subject on VEGF inhibitor therapy.

11. History of bleeding diathesis or clinically significant bleeding within 14 days prior to treatment with rivoceranib

12. History of clinically significant thrombosis within 3 months prior to treatment with rivoceranib that, in the Investigator's opinion, may place the subject at risk of side effects from anti-angiogenesis products

13. Therapy with systemic anticoagulant or antithrombotic agents within 7 days prior to treatment with rivoceranib that in the Investigator's opinion could interfere with clotting. The maximum allowable daily dose of aspirin is 325 mg

14. Gastrointestinal malabsorption, or any other condition that in the opinion of the Investigator might affect the absorption of rivoceranib

15. History of clinically significant glomerulonephritis, biopsy-proven tubulointerstitial nephritis, crystal nephropathy, or other renal insufficiencies

16. An uncontrolled intercurrent illness including, but not limited to any of the following:

a. Ongoing or active infection (including minor localized infections) requiring oral or intravenous treatment

b. Symptomatic class 3 or 4 congestive heart failure, defined as a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood

c. Unstable angina pectoris

d. Cardiac arrhythmia

e. Any other illness or condition that the treating Investigator feels would interfere with study compliance or would compromise the subject's safety or study endpoints

Ethical/Other

17. A female subject who is pregnant or breast-feeding

18. Psychiatric illness/social situations that would limit compliance with study requirements

19. History of drug or alcohol abuse within past 5 years

20. Known seropositive requiring anti-viral therapy for human immunodeficiency virus (HIV) infection

21. Known seropositive requiring anti-viral therapy for hepatitis B virus (HBV) infection OR evidence of active hepatitis B infection by detectable viral load if the antibody tests are positive

Note: A positive hepatitis B core antibody (HBcAb) subject with an undetectable surface antigen and negative hepatitis B DNA test (e.g., polymerase chain reaction [PCR] test) can be enrolled

22. Known seropositive requiring anti-viral therapy for hepatitis C virus (HCV) infection OR subjects with positive hepatitis C virus antibody

Note: A positive Anti-HCV subject with an undetectable/negative hepatitis C RNA test can be enrolled

23. Participation in another clinical study with any investigational medication or product administered within ≤28 days prior to first dose of rivoceranib

24. Subjects unable or unwilling to discontinue excluded medications for at least 5 half-lives prior to first dose of study drug

6. STUDY TREATMENT

6.1. Identity and Storage

Rivoceranib will be supplied by Elevar Therapeutics, Inc. Rivoceranib tablets will be packaged in polyvinylidene chloride (PVDC), heat-sealed foil-laminated blister packs. The outer packaging and the relevant unit of each pack of rivoceranib will be labelled according to the applicable law to indicate rivoceranib is to be used only for investigational purposes.

Rivoceranib is supplied as 100 mg and 200 mg film-coated tablets (Table 3).

Table 3: Identity of Rivoceranib Study Drug

Generic Name (INN) **USAN**	Rivoceranib Rivoceranib/rivoceranib mesylate
Other Names	Apatinib, apatinib mesylate
Chemical Name	N-(4-(1-cyanocyclopentyl)phenyl)-2-(4-pyridinylmethyl) amino-3- pyridinecarboxamide methanesulfonate
Molecular Formula	$C_{25}H_{27}N_5O_4S$
Compound Code	YN968D1
Molecular Weight	493.58

Rivoceranib should be kept in a locked storage area at 15–25°C (59–77°F) with excursions allowed to 40°C (104°F) for up to 24 hours. Investigators or designated personnel should check the temperature of the storage room daily and ensure that temperature monitoring devices are working correctly. Any deviations from the storage condition, including any actions taken, must be documented and reported to the Sponsor or designee. Once a deviation is identified, the study drug must be stored separately and not used until the Sponsor or designee provides written permission to use the study drug.

6.2. Preparation and Administration

Rivoceranib will be administered orally, once a day, approximately 1 hour after a meal and with water to facilitate swallowing. It is recommended that the administration time should be consistent throughout the study period (i.e., the administration interval should be approximately 24 hours with allowance of up to 18 hours apart due to clinic visit scheduling). To enable changes in dosage or dose interruption upon evaluation of subject's status, the study drug should not be taken until after Investigator instructions are received on days when a clinic visit occurs. If a dose is delayed by more than 6 hours, it should be skipped.

Subjects should take all tablets for the daily dose at one time. If the subject vomits after swallowing the study drug, the dose will not be replaced and there will be no replacement of a missed daily dose of drug.

6.3. Accountability and Compliance

The Investigator and/or the designated person responsible for dispensing study drugs must be able to account for all study drug provided to the site. The person responsible for dispensing the study drug must document the dispensing detail (the subject number, the date, the amount of dispensed study drug, the lot number of rivoceranib, etc.). Dose modification, interruptions, and reason for these actions must be recorded in the source documents. Subject compliance must also be recorded in source documentation. No study drug is to be used other than for this study.

Subjects are required to bring all blister packs, any unused study drug, and empty blister packs when they visit the site at the end of each cycle. The study drug returned by subjects or any unused study drug (that is, never dispensed to any subject) can be destroyed on site or at the depot according to institutional policies, after receiving Sponsor approval.

6.4. Concomitant Therapy

6.4.1. Excluded therapy

The following medications are considered exclusionary during the treatment period of the study. If any of these treatments/medications are administered, the subject may be required to be withdrawn from the treatment with rivoceranib. The Medical Monitor should be consulted if there are concerns or questions clarifying these therapies.

- Other anticancer therapy, systemic chemotherapy, radiotherapy (radiation as a palliative therapy to treat bone metastasis will be allowed), immunotherapy, cancer-related hormone therapy (cancer unrelated alternative hormone therapy that was initiated prior to the study enrollment is allowed) or herbal medicines that have official indication as anticancer drugs, or administration of investigational agents from other clinical studies.
- Medications known or suspected to prolong the QT/QTc interval, except for drugs with low risk of QT/QTc prolongation. This includes but is not limited to the following drugs:
  - antibacterial drugs: clarithromycin, azithromycin, erythromycin, roxithromycin, metronidazole, moxifloxacin
  - antiarrhythmic drugs: quinidine, sotalol, amiodarone, disopyramide, procainamide
  - antipsychotics: risperidone, fluphenazine, droperidol, haloperidol, thioridazine, pimozide, olanzapine, clozapine
  - antifungals: fluconazole, ketoconazole
  - antimalarials: mefloquine, chloroquine
  - antidepressants: amitriptyline, imipramine, clomipramine, dothiepin, doxepin

- antiemetic drugs: chlorpromazine, droperidol, metoclopramide, promethazine, dolasetron,
- , ondansetron

- All herbal supplements (including St John's wort)
- Food and drinks that contain grapefruit, Seville oranges or orange marmalade
- Strong inducers or inhibitors of CYP3A4 and CYP2D6 should be avoided. This includes but is not limited to the drugs listed in Appendix 9 (Table 17, Table 18).
- Substrates of CYP3A4, CYP2C9 and CYP2C19 with a narrow-therapeutic index should be avoided. This includes but is not limited to the drugs listed in Appendix 9 (Table 19).

In case a prohibited medication without a safer alternative is mandatory to treat an AE and it would make it unsafe to continue rivoceranib, the subject will be withdrawn from rivoceranib.

6.4.2. Allowed Therapy

Medications for treatment of underlying non-cancer disease and symptomatic treatment of AEs are permitted.

Packed red blood cell transfusion or erythropoietin therapy can be used after the initiation of the treatment at the Investigator's discretion; use must be recorded in the eCRF. Prophylactic use of anti-diarrheal and anti-nausea medications that are not excluded are permitted at the Investigator's discretion. Prochlorperazine, dronabinol, lorazepam, and granisetron uses are allowed in order of priority as an antiemetic therapy.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor, if required.

6.5. Dose Modification

Adverse events will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Individual subject treatments may be modified or interrupted based on observed hematologic and nonhematologic toxicities when the Investigator judges the toxicities to be at least possibly related to rivoceranib treatment.

Investigators should ultimately manage dose modification for individual subjects based on clinical judgement and are encouraged to discuss cases that are not clear with the Medical Monitor. Modifications may be performed based on the grade of toxicity as outlined in Appendix 8 (Table 10). Separate management guidelines for hypertension, proteinuria, oral mucositis, palmar-plantar erythrodysesthesia (hand-foot syndrome), gastrointestinal perforation, and ejection fraction decrease as a measure of congestive heart failure are located in Appendix 8 (Table 11 to Table 16).

Rivoceranib dose interruption up to 21 consecutive days is allowed for adverse events to improve or resolve.

Dose reduction should be limited to once every administration cycle (28 days/cycle) and reductions are permitted as outlined in Table 4 unless discussed and agreed upon between the Investigator and the Medical Monitor. A total of three dose reductions are permitted; however, dose reductions below 200 mg QD will not be permitted. Additional dose reductions based on Investigator's clinical judgement are permitted if discussed and agreed upon with the Medical Monitor.

A dose reduction skipping one dose level down to the next level is permitted if discussed and agreed upon with the Medical Monitor.

If dose is reduced down by skipping one dose level, the dose can be resumed at one immediate level up (skipped level) based on patient's tolerance and Investigator's clinical judgement and upon discussion with the Medical Monitor.

Table 4: Recommended Dose Modification Levels for Management of Rivoceranib Toxicity

Starting Dose	700 mg QD
Dose Level -1	500 mg QD
Dose Level -2	300 mg QD
Dose Level -3	200 mg QD

6.6. Dose Delays and Missed Doses

Subjects should be instructed to take rivoceranib tablets at a time that is approximately 24 hours after the last dose. If there is a delay of more than 6 hours after the time that the rivoceranib is normally taken, the dose should be skipped, and the subject should resume regular dosing with the next scheduled dose. Individual doses should not be taken less than 18 hours apart. Subjects should also be instructed not to double the next dose following a missed dose. If the subject vomits a dose, they must not take an additional dose.

6.7. Treatment Beyond Progressive Disease

Rivoceranib may be continued in the setting of progressive disease (PD) from first assessment of PD as long as the subject does not meet any of the rivoceranib discontinuation criteria

(Section 4.3.4) and all of the following criteria are met:

- Assessment of clinical benefit
- Absence of clinical symptoms or signs indicating clinically significant PD
- No decline in ECOG performance status
- Absence of rapid PD or threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention

- The subject is tolerating current dose of rivoceranib well (e.g., no significant high-grade toxicities)

If the lesions included in the tumor burden subsequently regress to the extent that the criteria for PD are no longer met, then treatment may continue according to the treatment schedule.

However, rivoceranib should be discontinued if repeat scans between 4 to 8 weeks later demonstrate PD by RECIST Version 1.1 compared to the subject's nadir, there is a deterioration in ECOG performance status, or clinical deterioration due to presumed progression. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment and could be discussed with the Medical Monitor if needed.

Subjects with PD who are eligible to continue receiving study therapy will be made aware of the potential benefits and risks of continuing treatment in the setting of PD and must provide a separate written informed consent prior to treatment.

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA in Section 1.3.

7.1. Efficacy Assessments

ORR, OS, PFS, DoR and TTP will be determined.

7.1.1. Tumor Evaluation

7.1.1.1. RECIST Version 1.1

The primary assessment of tumor response will be based on RECIST Version 1.1 (Eisenhauer, 2009; Appendix 6) and will be performed according to the schedule in the SoA (Section 1.3). On-treatment scans will be performed every 8 weeks (regardless of dose interruptions) for the first year and then approximately every 12 weeks (regardless of dose interruptions) and at EOT. Additional tumor assessments may be performed as clinically indicated.

At screening, a computed tomography (CT) scan with contrast of the neck, chest, abdomen and pelvis will be performed. Magnetic resonance imaging [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, Prior history of bone involvement or CNS involvement. A standard of care scan (even if performed before obtaining consent) may be used for the screening visit if within the visit window. The same imaging modality should be used throughout the study at the following time points or as clinically indicated:

- Within 28 days before Cycle 1 Day 1 (baseline measurement)
- End of Cycle 2 (prior to scheduled assessments and dosing on Cycle 3 Day 1)
- At 8 ± 1 week during the first year (prior to scheduled assessments and dosing on Day 1 of the subsequent visit) and 12 ± 1 weeks (prior to scheduled assessments and dosing on Day 1 of the subsequent visit) thereafter (regardless of any dose interruptions)
- EOT

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. All the baseline scans using the same imaging modality will be repeated at each follow-up visit at above mentioned timepoints after 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.

A change of imaging equipment will be allowed only if subject become hypersensitive to the contrast medium for CT or if there is concern about too much radiation exposure. In addition to these planned tumor evaluations, unscheduled imaging is allowed as clinically indicated at the Investigator's discretion. The images to be used for determination of disease progression will be reviewed by the Investigator or local imaging facility based on objective tumor assessments using the RECIST Version 1.1 guidelines. All scans should be available for submission to central archiving and independent central review.

Efficacy assessment will also be performed by Independent Central Review as per the Imaging Charter.

7.2. Safety Assessments

Safety assessments will consist of monitoring and recording of all AEs and serious adverse events (SAEs) using CTCAE Version 5.0 (APPENDIX 7), laboratory evaluation; regular performance of ECOG performance status (APPENDIX 3), physical examinations and vital sign measurements; and periodic ECGs. Planned time points for all safety assessments are provided in the SoA in Section 1.3.

7.2.1. 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.

7.2.2. Physical Examinations

Physical examinations will be performed according to the SoA in Section 1.3.

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 symptoms.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.2.3. Vital Signs

Vital signs (blood pressure, temperature, heart rate, pulse-oximetry and respiratory rate) according to the schedule in Section 1.3.

Vital signs will be measured in a seated or recumbent position after at least 5 minutes rest.

7.2.4. Electrocardiograms

ECGs will be recorded at the specified timepoints and will correspond with the pharmacokinetic blood draw(s) as specified in the SoA in Section 1.3.

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.

7.2.5. Clinical Safety Laboratory Assessments

Routine clinical laboratory tests (serum chemistry, hematology, urinalysis, coagulation, thyroid and pregnancy tests) will be performed in a local laboratory according to the SoA in Section 1.3 and APPENDIX 2.

The Investigator must review the laboratory report, document the review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

7.3. Adverse Events and Serious Adverse Events

The definitions of an AE, SAE, and suspected unexpected serious adverse reactions (SUSAR) can be found in APPENDIX 4.

Safety assessments will include monitoring and recording AEs and SAEs.

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

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and are responsible for reporting AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject

to discontinue rivoceranib or the study promptly and perform any testing to make a diagnosis. (Section 7).

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

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.

Investigator Follow-Up

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4. Every effort should be made to follow all SAEs until a final outcome can be reported. During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the subject's medical record to facilitate source data verification.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to rivoceranib or study participation, the Investigator must promptly notify the Sponsor.

All pregnancies reported during the study should be followed per APPENDIX 5.

Sponsor Follow-Up

For SAEs and pregnancies, the Sponsor or a designee may follow up by telephone, fax,

electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries) in order to perform an independent medical assessment of the reported case.

Adverse Events That Occur after the Adverse Event Reporting Period

After the end of the AE reporting period (defined as 30 calendar days after stopping of treatment with rivoceranib or until initiation of new, non-protocol specified systemic anticancer therapy, whichever occurs first for AEs), all deaths, regardless of cause, should be recorded on the applicable eCRF as described in Section 7.3.5.

In addition, if the Investigator becomes aware of a SAE that is believed to be related to prior exposure to rivoceranib, the event should be reported either by faxing or by scanning and emailing

the paper Serious Adverse Event form using the fax number or email address provided to Investigators (see Recording and Follow-Up of AE and/or SAE in Appendix 4).

7.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Investigators will seek information on AEs at each subject contact. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event eCRF.

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

7.3.3. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met. Reporting should take place within 24 hours after the Investigator learns of the event.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.4. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment and until 30 days after the last dose of rivoceranib.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in APPENDIX 5.
- While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes
- (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Pregnancy tests may be performed more frequently if required by local regulatory authorities and informed consent forms (ICFs) will be updated accordingly.

7.3.5. Deaths

All serious AEs with death as an outcome that occur during the AE reporting period, regardless of relationship to treatment with rivoceranib, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical event on the Adverse Event eCRF. Generally, only one such event should be reported.

Deaths that occur after the AE reporting period should be reported as described in Section 7.3.1.

7.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Events due to disease progression alone will not be considered as an AE or SAE. For other non-qualifying AE definitions, refer to APPENDIX 4.

7.3.7. Treatment of Overdose

For this study, any dose of study treatment greater than prescribed within a 30-hour time period from previous dose will be considered an overdose. The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow-up until resolution.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

If the overdose results in an AE, the AE must also be recorded on the AE eCRF. Overdose does not automatically make an AE serious; however, if the consequences of the overdose meet any of the serious criteria under an SAE (APPENDIX 4) the event should be reported as such.

Decisions regarding dose interruptions or modifications after an overdose will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

7.4. Exploratory Assessments

7.4.1. Pharmacokinetics

Whole blood samples will be collected from all subjects at each time point for measurement of plasma concentrations of rivoceranib as specified in the SoA (Section 1.3) and in Table 5.

In addition, an intensive pharmacokinetic (PK) sampling will be done in up to 12 subjects. Additional samples will be collected as specified in the SoA (Section 1.3) and in Table 5. Collection, handling and storage of blood samples for determination of plasma PK profiles of rivoceranib will be explained in the Central Laboratory Manual.

Table 5: Pharmacokinetic Blood Sample Collection Log for Rivoceranib

PK Sampling for All Subjects	
Visits	**Time Points**
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)
Intensive PK Sampling for up to 12 Subjects at Selected Study Sites	
Visits	**Time Points**
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)
Abbreviations: h=hour; min=minute; PK=pharmacokinetic	

Plasma concentrations of rivoceranib will be determined using a validated combined liquid chromatography-mass spectrometry method. The following PK parameters will be calculated: maximum observed serum concentration (C_{max}), time of peak concentration (T_{max}), area under the serum concentration-time curve (AUC), clearance (CL/F) and terminal elimination half-life ($t_{1/2}$).

The plasma samples remaining after analysis will be stored for up to 10 years after the end of the study and then destroyed, unless other time limitations are required by local regulations or ethical requirements.

7.4.2. Biomarkers

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. Tumor samples remaining after analysis will be stored for up to 10 years after the end of the study and then destroyed, unless other time limitations are required by local regulations or ethical requirements. Refer to the Central Laboratory Manual for the handling of tumor tissue samples.

7.4.3. Quality of Life Assessments

Subjects will complete a Functional Assessment of Cancer Therapy (FACT)-G questionnaire according to the planned time points provided in the SoA in Section 1.3.

7.4.4. Disease Control Rate

Disease control rate 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 tumor assessment.

7.4.5. Objective Response Rate (ORR) per Exploratory Assessments

Independent Central Review will evaluate the ORR in exploratory assessment, the proportion of subjects who achieve confirmed CR or PR per CHOI criteria.

The scans assessed using RECIST criteria will also be assessed using CHOI criteria by Independent Central Review per Imaging Charter. Freehand measurement of tumor is preferred but circular is permitted (Appendix 10).

8. STATISTICAL CONSIDERATIONS

Data collected in this study will be presented descriptively using summary tables, figures and data listings. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Missing value will not be imputed unless otherwise stated.

8.1. 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.

8.2. Populations for Analyses

8.2.1. Safety Population

The safety population will include all subjects enrolled in the study who received at least one dose of rivoceranib.

8.2.2. Efficacy Evaluable Population

The efficacy evaluable population consisting of eligible subjects treated with at least one dose of rivoceranib who have at least one post baseline tumor assessment will be used for the primary and secondary analysis of efficacy data. Subjects who discontinued treatment due to disease progression will also be included in the efficacy population.

8.2.3. Exploratory Population

PK analysis population includes all subjects who receive rivoceranib and for whom valid plasma concentration can be determined.

Biomarker population includes all subjects who receive rivoceranib and have evaluable tissue samples.

Quality of life population includes all subjects with at least one evaluable patient reported outcome.

CHOI criteria population includes all eligible subjects treated with at least one dose of rivoceranib who have at least one post-baseline tumor assessment.

Disease control rate population includes all eligible subjects treated with at least one dose of rivoceranib who have at least one post baseline tumor assessment. Subjects who discontinued treatment due to disease progression will also be included in this population.

8.3. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Additional analysis populations, which may be used in sensitivity analyses for primary and secondary efficacy objectives and for analyses of exploratory objectives, will be defined in the statistical analysis plan.

8.3.1. Efficacy Analyses

Efficacy analyses will be based on the efficacy evaluable populations (see APPENDIX 6) for RECIST Version 1.1 criteria.

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

Analysis of the Primary Efficacy Endpoint(s).

The primary efficacy endpoint is the objective response rate (ORR) defined as the proportion of subjects who achieve confirmed complete response (CR) or partial response (PR) per RECIST Version 1.1. The ORR will be evaluated separately by investigator/institutional assessment and by Independent Central Review. The ORR will be summarized with frequencies and percentages. The exact 95% CI will be constructed for the ORR using an exact binomial method. Subjects not meeting the criteria for CR or PR, including those without any post-baseline tumor assessments, will be considered as non-responders.

Analysis of Secondary Efficacy Endpoint(s)

Overall survival (OS) will be assessed at 1 year and 2 years for survival for up to 2 years, or until withdrawal of consent, lost to follow-up, or death, whichever occurs first. At the time of analysis of OS, any subjects who remain alive will be censored at the last date they were known to be alive. The OS will be computed using the Kaplan-Meier method.

Progression free survival (PFS) is the time from the start of treatment with rivoceranib to the first evaluation showing PD or death, whichever occurs first. Subjects who do not experience PD or death will be censored at the date of last disease assessment. PFS will be assessed at 6 months, 12 months and 2 years. The PFS will be summarized using the Kaplan-Meier methodology. The PFS will be evaluated separately by investigator/institutional assessment and by Independent Central Review.

Duration of response (DoR) is the proportion of subjects who achieve a CR or PR based on RECIST criteria and defined as the interval between the date of initial documentation of a response and are confirmed with the same or better response at the immediate next tumor assessment disease progression or death from any cause, whichever occurs first and are confirmed with the same or better response at the immediate next tumor assessment. The DoR will be summarized with frequencies and percentages. A 95% CI will be constructed for DoR using an exact binomial method. The DoR will be evaluated separately by investigator/institutional assessment and by Independent Central Review.

Time to progression (TTP) is the length of time from the start of treatment with rivoceranib until objective tumor progression. 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. The TTP will be estimated using the Kaplan-Meier method. The TTP will be evaluated separately by investigator/institutional assessment and by Independent Central Review.

8.3.2. Safety Analyses

Safety analyses will be based on the safety population. Safety will be assessed based on incidence of AEs, changes in laboratory test results, vital signs, 12-lead ECG findings, and physical examination findings.

8.3.2.1. Extent of Exposure

The number of doses, number of cycles, duration of dosing, total dose (mg) of rivoceranib administrated will be summarized. Dose modifications and deviations will be flagged.

8.3.2.2. Adverse Events

Adverse events will be coded by preferred term and system organ class using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and graded according to CTCAE. Any events occurring following study drug administration or increasing in severity will be counted as treatment-emergent adverse events (TEAEs). Incidence of TEAEs will be summarized as follows:

- All AEs
- All Grade 3/4/5 AEs
- All drug-related AEs
- All AEs leading to rivoceranib or study discontinuations
- All serious AEs, including those with death as outcome

8.3.2.3. Clinical Laboratory

Laboratory results (hematology, serum chemistry and coagulation) and the corresponding change from baseline values will be summarized. A shift table, tabulation for baseline to each scheduled assessment and the worst post treatment value according to the CTCAE grade, will be provided for selected clinical laboratory tests. Laboratory results together with the normal ranges and CTCAE grade will be listed. Laboratory values that are below or above the normal ranges will be flagged.

8.3.2.4. Vital Signs and ECG

Vital signs and ECGs and the corresponding changes from baseline will be summarized.

8.3.3. Exploratory Analyses

A separate statistical analysis plan (if performed) will outline details of the PK and biomarker analyses. Correlative biomarker analyses in tumor tissues will be performed. Patient reported outcomes will be assessed using the FACT-G questionnaire. The scores from these questionnaires will be summarized by study visit using descriptive statistics.

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 tumor assessment. DCR (CR+PR+stable disease) will be summarized with frequencies and percentages. A 95% CI will be constructed for DCR using an exact binomial method. The DCR will be evaluated separately by investigator/institutional assessment and by Independent Central Review.

Objective response rate (ORR) per exploratory assessment, defined as the proportion of subjects who achieve confirmed CR or PR per CHOI criteria, will be evaluated by Independent Central Review. The ORR will be summarized with frequencies and percentages. The exact 95% CI will be constructed for the ORR using an exact binomial method.

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APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D-Responsibilities of Sponsors and Investigators)
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects. In cases of a deviation from the approved study protocol, the deviation will be reported to the Sponsor and IRB/IEC as soon as possible
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

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

Informed Consent Process

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

- Subjects must be informed that their participation is voluntary, and they may elect to discontinue treatment or withdraw from the study at any time for any reason without negative recourse. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative in a language the subject or the subject's authorized representative can understand.
- Subjects who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the use of remaining samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research.

Data Protection

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

Dissemination of Clinical Study Data

All subject medical information obtained during the conduct of this study is confidential. The Sponsor and the Investigator are responsible for ensuring that subject anonymity is maintained, and subject identity is protected from unauthorized disclosure.

Access to a subject's medical data for source data verification by monitors, auditors and inspectors requires the subject's written authorization in the ICF to use and disclose his/her personal health information if permitted or required by law. Medical information may be given

to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national regulatory agencies; national and local health authorities; Sponsor medical monitors, representatives, and collaborators; and the IRB/IEC for each study site.

Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by Elevar Therapeutics, Inc. or its designee. Data will be reviewed for accuracy and completeness by Elevar Therapeutics, Inc. or its representatives during and after onsite monitoring visits, and any discrepancies will be resolved with the Investigator or designees as appropriate.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in but not limited to hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, and screening and enrollment logs.

Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

Publication Policy

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

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

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

APPENDIX 2: CLINICAL LABORATORY TESTS

The tests in Table 6 will be performed at the visits specified in the SoA (Section 1.3) by the local laboratory. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Investigators must document their review of each laboratory safety report.

Table 6: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameter
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) • 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 Tests	• prothrombin time (PT) or international normalized ratio (INR) • partial thromboplastin time (PTT) or activated PTT (aPTT)

Laboratory Assessments	Parameter
Serological Tests[b]	• 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
Pregnancy Tests for WOCBP	• 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.] Only tested at screening

[c.] Serological test results obtained within 2 years of study enrollment may be used

APPENDIX 3 ECOG PERFORMANCE STATUS

Table 7: ECOG Performance Score

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

Abbreviations: ECOG=Eastern Cooperative Oncology Group

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655

APPENDIX 4 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
An AE is any untoward medical occurrence regardless of causal attribution in a subject administered a pharmaceutical product in a clinical trial. An AE can be any of the following: • Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product • Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) • Recurrence of an intermittent medical condition not present at baseline • Any clinically significant deterioration in a laboratory value or other clinical test that is associated with symptoms or leads to a change in rivoceranib or concomitant treatment or discontinuation from rivoceranib • AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of rivoceranib, such as tumor biopsies

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical event.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

Definition of SUSAR

SUSAR Definition:

- Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to rivoceranib and are both unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. SUSARs are subject to expedited reporting by the Sponsor to the appropriate regulatory authorities.
- It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the Investigator of the SUSAR as soon as possible.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF, and report to the Sponsor in accordance with instructions provided in this section and Section 7.3. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice and elevated transaminases) should be recorded. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis. (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories according to NCI-CTCAE Version 5.0 (APPENDIX 7): • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • Life-threatening consequences • Death related to AE An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered related to rivoceranib, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:
  - Temporal relationship of event onset to the initiation of rivoceranib therapy
  - Course of the event, with special consideration of the effects of dose reduction, discontinuation of rivoceranib, or reintroduction of rivoceranib (as applicable)
  - Known association of the event with rivoceranib or with similar treatments
  - Known association of the event with the disease under study
  - Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
  - Presence of non-treatment-related factors that are known to be associated with the occurrence of the event
- The attribution code describes, in the opinion of the Investigator, how likely it is that the adverse event is due to protocol treatment:
  - 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.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

SAE Reporting via Paper CRF

- The primary mechanism for reporting an SAE will be the paper SAE CRF form. The site will report all SAEs within 24 hours of awareness using the paper SAE CRF form.
- Email or facsimile transmission of the paper SAE CRF is the preferred method to transmit this information to Sponsor, or designee.
- In rare circumstances and in the absence of email or facsimile equipment, notification by telephone is acceptable.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

APPENDIX 5: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP

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

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

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Women

WOCBP who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (See Table 8 for recommended methods of contraception).

A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly.

WOCBP must use contraception from the time of screening and must agree to continue using such precautions for 30 days after the last dose of rivoceranib. Cessation of birth control after this point should be discussed with a responsible physician.

Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette® (desogestrel) which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 8: Highly Effective Methods of Contraception (<1% Failure Rate)

Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®[a])	• Etonogestrel implants; e.g., Implanon® or Norplan® • Intravaginal device; e.g., ethinylestradiol and etonogestrel • Medroxyprogesterone injection, e.g., Depo-Provera® • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette® (desogestrel)

[a] This is also considered a hormonal method.

Men

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom with spermicide where locally available from Day 1 and for 30 days after the final dose of rivoceranib. It is strongly recommended that the female partner of childbearing potential to use at least one highly effective method of contraception (Table 8). Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

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

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to

8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 7.3.4. While the Investigator is not obligated to actively seek this information in former study subject, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue rivoceranib or be withdrawn from the study.

APPENDIX 6: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

Evaluation of Target Lesions

- **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes).
- **Partial Response** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- **Stable Disease** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response** - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-complete response/Non-progressive disease** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see Section 4.3.4). In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' or an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST Version 1.1. According to the protocol, subjects may continue to receive rivoceranib therapy if Investigators consider that subjects continue to benefit from treatment (Section 6.7).

Evaluation of Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The subject's best overall

response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Table 9 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 9: Evaluation of Overall Response

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.

APPENDIX 7: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 5.0

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, published

27 November 2017) provides descriptive terminology to be used for adverse event reporting in the clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE Version 5.0 have been correlated with single-concept MedDRA terms.

The CTCAE Version 5.0 grading refers to the severity of the AE. The CTCAE Grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

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

Abbreviations: ADL=activities of daily living, CTCAE=Common Terminology Criteria for Adverse Events.

[a.] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b.] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

For further details regarding MedDRA, refer to the MedDRA website at: http://www.meddra.org.

APPENDIX 8: MANAGEMENT GUIDELINES FOR TOXICITIES

Table 10: Rivoceranib Treatment-related Adverse Event Management

* Use specific separate management guidelines for rivoceranib-related AEs of hypertension, proteinuria, oral mucositis, palmar-plantar erythrodysesthesia (hand-foot syndrome), and for rivoceranib-class effect AEs of gastrointestinal perforation, and ejection fraction decrease as a measure of congestive heart failure.		
• Rivoceranib dose interruption up to 21 days is allowed for adverse events to improve or resolve. • *Investigators should ultimately manage dose modification for individual subjects based on clinical judgement and are encouraged to discuss cases that are not clear with the Medical Monitor.*		
Grade of Adverse Event (NCI CTCAE Version 5.0)	**Management**	**Follow-Up**
Grade 1[a]	• Use local practice to manage the AE[b] • Continue treatment without dose adjustment	**If persistent:** • Treat as Grade 2
Grade 2[a]	• Use local practice to manage the AE[b] • Rivoceranib may be pre-emptively dose reduced by one level at any time during the current cycle or in the next cycle	**If persists for >4 weeks or worsens:** • Contact Medical Monitor **Nonhematologic AE:** **If improves to ≤ Grade 1 within 4 weeks:** • Resume rivoceranib at the dose before reduction or at the pre-emptively reduced dose **Hematologic AE:** **If improves to ≤ Grade 1 or baseline within 4 weeks:** • Resume rivoceranib at the dose before reduction or continue at the pre-emptively reduced dose
Grade 3-4[a]	• Use local practice to manage the AE[b] • Temporarily withhold rivoceranib	**If persists for >3 weeks:** • Contact Medical Monitor **Nonhematologic AE:** **If improves to ≤ Grade 1 or manageable Grade 2 within 3 weeks:** • Resume rivoceranib at dose reduced by one level **Hematologic AE:** **If improves to ≤ Grade 1 or baseline within 3 weeks:** • Resume rivoceranib at dose reduced by one level

Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute

[a] Refer to NCI-CTCAE Version 5.0 for term-specific grading criteria.

[b] Contraindicated concomitant medications should not be given unless benefit outweighs the risk per the Investigator's judgement.

Table 11: Hypertension AE Management

- Rule out other cardiovascular causes and other offending agents.
- With the new-onset hypertension of any grade, monitor CBC, urinalysis and serum creatinine to assess presence of worsening renal function, proteinuria, hemolytic anemia or thrombocytopenia.
- Preferred antihypertensive agents for angiogenesis inhibitor-associated hypertension include: ACE inhibitors and dihydropyridine calcium channel blockers. Diltiazem and verapamil are prohibited due to strong CYP3A4 inhibition.
- *Investigators should ultimately manage dose reduction or modification for individual subjects based on their clinical judgement and are encouraged to discuss with the medical monitor in cases that are not clear.*

Grade of Hypertension (NCI CTCAE Version 5.0)	**Management**	**Follow-Up**
Grade 1: Systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg[a]	• Continue blood pressure monitoring and rivoceranib therapy without dose adjustment	**If diastolic BP >20 mmHg from baseline:** • Treat as Grade 2
Grade 2: Systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg[a]	• If new-onset hypertension, initiate antihypertensive medication • Titrate dose of antihypertensive medication to goal of diastolic blood pressure ≤20 mmHg from baseline • Consider daily blood pressure home monitoring if subject has ≥2 cardiovascular risk factors • Continue rivoceranib therapy without dose adjustment	**If diastolic BP >20 mmHg from baseline for >1-2 weeks:** • Start daily blood pressure home monitoring • Assess and titrate therapeutic dose of antihypertensive medication. Consider more than one drug or more intensive antihypertensive therapy. • If symptomatic or if adequate antihypertensive treatment does not provide control, may consider rivoceranib dose reduction per protocol. • Discuss with Medical Monitor as needed
Grade 3: Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg[a]	• Start daily home blood pressure monitoring • If new-onset hypertension, initiate antihypertensive medication. Consider titration to more than one drug or more intensive antihypertensive therapy • Titrate dose of antihypertensive medications to goal of diastolic blood pressure ≤20 mmHg from baseline. • Temporarily withhold rivoceranib therapy if adequate antihypertensive interventions do not provide control	**If symptomatic or if diastolic BP >20 mmHg from baseline for >3 weeks** • Contact Medical Monitor **If improves to diastolic BP ≤20 mmHg from baseline within 3 weeks:** • Continue daily blood pressure home monitoring • Assess and titrate therapeutic level of antihypertensive medications • Resume rivoceranib therapy at dose reduced by one level per protocol. • Discuss with Medical Monitor as needed
Grade 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)[a]	• Discontinue rivoceranib therapy per protocol • Urgent hospitalization • Discuss with Medical Monitor as needed	**Follow-up until resolved**

Abbreviations: ACE=angiotensin converting enzyme; BP=blood pressure; CBC=complete blood count; CTCAE=common terminology criteria for adverse events; NCI=National Cancer Institute

[a.] Refer to NCI-CTCAE Version 5.0 for term-specific grading criteria

Table 12: Proteinuria AE Management

- Rule out functional causes of proteinuria (fever, emotional stress, heavy physical exercise, acute illness), pre-existing renal issues, kidney infections, diabetes, hypertension and other offending agents (NSAIDs).
- *Investigators should ultimately manage dose reduction or modification for individual subjects based on their clinical judgement and are encouraged to discuss with the medical monitor in cases that are not clear.*

Grade of Proteinuria (NCI CTCAE Version 5.0)	**Management**	**Follow-Up**
Grade 1: 1+ proteinuria; urinary protein <1.0 g/24 hrs[a]	• Assess blood pressure and blood glucose control • Continue rivoceranib therapy without dose adjustment	**If persistent proteinuria:** • Treat as Grade 2
Grade 2: 2+ and 3+ proteinuria; urinary protein 1.0-3.4 g/24 hrs[a]	• Assess blood pressure and blood glucose control and consider blood pressure management with ACE inhibitor with caution due to risk of hyperkalemia • Continue rivoceranib therapy without dose adjustment • If accompanied by acute kidney injury, consider consult with nephrologist and temporary withhold rivoceranib	**If acute kidney injury is detected:** • Consider consult with nephrologist and temporarily withhold rivoceranib **If persists for >3 weeks without kidney injury:** • Consider temporary rivoceranib dose reduction per protocol **If improves to Grade 1 within 3 weeks:** • Continue rivoceranib therapy without dose adjustment • If rivoceranib therapy was withheld, resume at dose reduced by one level per protocol • Discuss with Medical Monitor as needed
Grade 3: 4+ proteinuria; urinary protein ≥3.5 g/24 hrs[a]	• Consult with nephrologist • Temporarily withhold rivoceranib therapy	**If persists for >3 weeks or worsens** • Discontinue rivoceranib therapy per protocol **If improves to Grade 1 within 3 weeks:** • Resume rivoceranib therapy at dose reduced by one level per protocol • Discuss with Medical Monitor as needed

Abbreviations: ACE=angiotensin converting enzyme; CTCAE=common terminology criteria for adverse events; hrs=hours; NCI=National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drug

[a.] Refer to NCI-CTCAE Version 5.0 for term-specific grading criteria

Table 13: Oral Mucositis AE Management

- Use gentle oral hygiene and regular inspection to prevent oral tissue injury. Avoid smoking, alcohol, and citrus, spicy, hot, crusty foods or drinks. Use bland non-alcoholic sodium bicarbonate containing mouth wash at least 4-6 times/day for prevention.
- *Investigators should ultimately manage dose reduction or modification for individual subjects based on their clinical judgement and are encouraged to discuss with the medical monitor in cases that are not clear.*

Grade of Oral Mucositis (NCI CTCAE Version 5.0)	**Management**	**Follow-Up**
Grade 1–2: Mild-Moderate pain; not interfering with oral intake[a]	• Consider nutritional support, oral decontamination, and other therapeutic interventions, and as clinically indicated[b] • Increase frequency of non-alcoholic sodium bicarbonate containing mouth wash up to each hour if necessary • For moderate pain, a topical NSAID (e.g. oral paste) can be considered[b] • Continue rivoceranib therapy without dose adjustment	**If persists for >3 weeks or worsens:** • Treat as Grade 3–4
Grade 3-4: Severe pain; interfering with oral intake; Life-threatening consequences; urgent intervention indicated[a]	• Consider nutritional support, oral decontamination, and other therapeutic interventions as clinically indicated • For ulcers, consider clobetasol gel or ointment or topical high potency corticosteroids mouth rinse • For severe pain, consider acetaminophen or paracetamol as maintenance therapy in combination with an immediate release oral opioid or fast acting fentanyl preparation (e.g. fentanyl nasal spray) to relief pain short term. More aggressive pain management may be considered to treat persistent severe pain[b] • Consider temporary rivoceranib dose reduction per protocol	**If persists for >1-2 weeks:** • Temporarily withhold rivoceranib therapy **If improves to Grade 1 within 3 weeks:** • If rivoceranib therapy was withheld, resume at dose reduced by one level per protocol • Discuss with Medical Monitor as needed

Abbreviations: CTCAE=common terminology criteria for adverse event; NCI=National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drug

[a.] Refer to NCI-CTCAE Version 5.0 for term-specific grading criteria.

[b.] Contraindicated concomitant medications should not be given unless benefit outweighs the risk per the judgment of the Investigator.

Table 14: Palmar-plantar Erythrodysesthesia Syndrome (Hand-Foot Syndrome)

AE Management

- Usually occurs between 1–4 weeks into VEGF inhibitor treatment and worse during the first 6 weeks of rivoceranib treatment.
- For all grades, avoid hot water and alcohol-containing hand products, wear thick cotton gloves and/or socks at night, and use moisturizing emollient creams. Urea cream can be used on calluses and hyperkeratotic areas.
- *Investigators should ultimately manage dose reduction or modification for individual subjects based on their clinical judgement and are encouraged to discuss with the medical monitor in cases that are not clear.*

Grade of Palmar-Plantar Erythrodysesthesia Syndrome (NCI CTCAE Version 5.0)	**Management**	**Follow-Up**
Grade 1: Minimal skin changes or dermatitis (e.g., erythema, edema or hyperkeratosis) without pain[a]	• Continue preventive measures and moisturizing topicals[b] • Continue rivoceranib therapy without dose adjustment	**If persists for >1-2 weeks or worsens:** • Treat as Grade 2
Grade 2: Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL [a]	• Continue preventive measures and moisturizing topicals[b] • Pain management with lidocaine gel or oral analgesics as needed (NSAIDs or acetaminophen or paracetamol)[b] • Consider topical antibiotics to treat blisters and erosions to prevent infection • Continue rivoceranib therapy without dose adjustment	**If persists for >1-2 weeks or worsens:** • Treat as Grade 3 • Discuss with Medical Monitor as needed
Grade 3: Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL[a]	• Continue preventive measures and moisturizing topicals[b] • If pain is not controlled with classical analgesics, GABA agonists or narcotics may be considered[b] • Use topical antibiotics and hydrocolloid dressings to treat blisters and erosions to prevent infection[b] • The use of topical calcineurin inhibitors (pimecrolimus, tacrolimus) are not recommended due to lack of efficacy. The role of topical steroids is also controversial. Although short-term application may be beneficial, extended application may result in aggravation of skin changes • Temporarily withhold rivoceranib therapy	**If persists for >1-2 weeks:** • Temporarily withhold rivoceranib therapy **If improves to Grade 1 within 3 weeks:** • Resume rivoceranib at dose reduced by one level per protocol. • Discuss with Medical Monitor as needed

Abbreviations: ADL=activity of daily living; CTCAE=Common Terminology Criteria for Adverse Event; NCI=National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drug; VEGF=vascular endothelial growth factor

[a.] Refer to NCI-CTCAE Version 5.0 for term-specific grading criteria.

[b.] Contraindicated concomitant medications should not be given unless benefit outweighs the risk per the judgment of the Investigator.

Table 15: Gastrointestinal Perforation AE Management

• Investigators should ultimately manage dose reduction or modification for individual subjects based on their clinical judgement and are encouraged to discuss with the medical monitor in cases that are not clear. Note: this is not an expected event for rivoceranib, but it is a drug class effect.		
Grade of Gastrointestinal Perforation (NCI CTCAE Version 5.0 terms: colonic perforation, duodenal perforation, esophageal perforation, gastric perforation, ileal perforation, jejunal perforation, rectal perforation, small intestinal perforation)	**Management**	**Follow-Up**
Grade 1: -	• Continue rivoceranib	
Grade 2: Invasive intervention not indicated	• Continue rivoceranib. Contact MM as needed.	• Resume when it resolves to baseline. If persists for 4 weeks despite clinical management then discontinue rivoceranib
Grade 3: Invasive intervention indicated	• Hold rivoceranib • Consult with gastroenterologist • Contact MM to discuss	• Resume when it resolves to baseline. If persists for 4 weeks despite clinical management then discontinue rivoceranib
Grade 4: Life-threatening consequences; urgent operative intervention indicated	• Discontinue rivoceranib	

Abbreviations: CTCAE=common terminology criteria for adverse events; NCI=National Cancer Institute; MM= Medical Monitor.

Table 16: Ejection Fraction Decrease AE Management

• Investigators should ultimately manage dose reduction or modification for individual subjects based on their clinical judgement and are encouraged to discuss with the medical monitor in cases that are not clear. Note: this is not an expected event for rivoceranib, but it is a drug class effect.		
Grade of Ejection fraction decreased (NCI CTCAE Version 5.0)	**Management**	**Follow-Up**
Grade 1: -	• Continue rivoceranib	
Grade 2: Resting EF 50%–40%; 10%–19% drop from baseline **Grade 3:** Resting EF 39%–20%; >=20% drop from baseline **Grade 4:** Resting EF <20%	• **If LVEF 45%–49% and decrease of <10 EF points from baseline:** Continue rivoceranib and repeat measurement in 3 weeks • **If LVEF 45%–49% and decrease 10 EF points from baseline:** Hold rivoceranib and repeat measurement in 3 weeks • **If LVEF 44%:** Hold rivoceranib and repeat measurement in 3 weeks	• **If LVEF ≤44% or LVEF 45%–49% and decrease of ≥10 EF points from baseline:** Discontinue rivoceranib • **LVEF 45%–49% and decrease of <10 EF points from baseline or LVEF>49%:** Resume rivoceranib

Abbreviations: CTCAE=common terminology criteria for adverse events; NCI=National Cancer Institute; EF=Ejection Fraction; LVEF=Left Ventricular Ejection Fraction.

APPENDIX 9: CYTOCHROME P450 KNOWN DRUG INTERACTION CHARTS

Table 17: Medications Metabolized by Cytochrome P450 3A4

INHIBITORS		SUBSTRATES*		INDUCERS
Strong (≥5-fold increase in level or >80% decrease in clearance)		**Macrolide Antibiotics**	**Miscellaneous**	**Strong**
atazanavir	itraconazole	clarithromycin	alfentanyl	efavirenz
boceprevir	ketoconazole	erythromycin	amiodarone	etravirine
darunavir	posaconazole	(not azithromycin)	aprepitant	nevirapine
delavirdine	voriconazole		bisoprolol	nelfinavir
efavirenz		**Anti-arrhythmics**	bosentan	ritonavir
fosamprenavir	cannabidiol	quinidine → 3-OH	bromocriptine	
indinavir	citalopram		buprenorphine	barbiturates
lopinavir	escitalopram	**Benzodiazepines**	buspirone	bosentan
nelfinavir	imatinib	alprazolam	cafergot	carbamazepine fosphenytoin
ritonavir	isoniazid	clobazam	caffeine	glucocorticoids
saquinavir	quinidine	clonazepam	calcitriol	modafinil
telaprevir		diazepam → 3-OH	carbamazepine	oxcarbazepine
	clarithromycin	midazolam	chloroquine	pentobarbital
	telithromycin	triazolam	citalopram	phenobarbital
	(not azithromycin)		colchicine	phenytoin
Moderate (≥2 to <5-fold increase in level or 50-80% decrease in clearance)		**Immune Modulators**	cocaine	primidone
amiodarone	grapefruit juice	cyclosporine	codeine	rifampin
amprenavir	haloperidol	tacrolimus	dapsone	rifabutin
aprepitant	lapatinib		dasatinib	
cimetidine	lidocaine	**HIV Antivirals**	dexamethasone	**Miscellaneous**
caffeine	miconazole	atazanavir	dihydroergotamine	clobazam
cyclosporine	norfloxacin	cobicistat	docetaxel	ethosuximide
desipramine	tetracycline	darunavir	doxepin	phenylbutazone
diltiazem	verapamil	fosamprenavir	doxorubicin	St. John's wort
doxycycline		indinavir	eletriptan	tipranavir
dronedarone		nelfinavir	ergotamine	topiramate
erythromycin		ritonavir	erlotinib	
fluconazole		saquinavir	fentanyl	
			finasteride	
Miscellaneous		**Antihistamines**	gleevec	
amlodipine	propranolol	chlorpheniramine	haloperidol	
cannabinoid	quinine		irinotecan	
chloramphenicol	ranitidine	**Calcium Channel Blockers**	lidocaine	
ciprofloxacin	sildenafil	amlodipine	marijuana	
cobicistat	starfruit	diltiazem	methadone	
danazol	ticagrelor	felodipine	nateglinide	
diethyldithiocarbamate	zafirlukast	nifedipine	ondanestron	
ergotamine		verapamil	pimozide	
ethinyl estradiol			quinine	
fluoxetine		**HMG CoA Reductase Inhibitors**	salmeterol	
fluvoxamine		atorvastatin	sildenafil	
marijuana		lovastatin	sirolimus	
nifedipine		simvastatin	tamoxifen	
norfluoxetine		(not pravastatin or rosuvastatin)	taxol	
olanzapine			tramadol	
paclitaxel		**Steroids**	trazodone	
pimozide		estradiol	vincristine	
		hydrocortisone	zopiclone	
		progesterone		
		testosterone		

*These medications may also alter the metabolism of methadone.

Note: Combination with quetiapine is contraindicated – the mechanism of interaction is thought to be via CYP 2D6 and p-glycoprotein (not via CYP3A4), and is therefore not listed in this table, but it is an important interaction.

Adapted from Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007).

Table 18: Cytochrome P450 2D6 Known Drug Interaction Chart

Drugs Metabolized by CYP2D6 Enzyme

ANALGESICS
codeine
hydrocodone
oxycodone
phenacetin
tramadol

ANESTHETICS
lidocaine

ANORECTICS
dexfenfluramine

ANTIEMETIC/PROKINETICS
metoclopramide
ondansetron

ANTIHISTAMINES
chlorpheniramine
promethazine

ANTINEOPLASTICS
tamoxifen

CARDIOVASCULAR
alprenolol
carvedilol
clonidine
debrisoquine
diltiazem
disopyramide
flecainide
S-metoprolol
mexiletine
nebivolol
perhexiline
propafenone
propranolol
sparteine
timolol

CHOLINESTERASE INHIBITORS
donepezil

COUGH SUPPRESSANT
dextromethorphan

PSYCHOTROPICS
amitriptyline
amphetamine
aripiprazole
atomoxetine
chlorpromazine
clomipramine
desipramine
duloxetine
fluoxetine
fluvoxamine
haloperidol
iloperidone
imipramine
methamphetamine
methoxyamphetamine
minaprine
nortriptyline
paroxetine
perphenazine
pimozide
risperidone
sertraline
thioridazine
venlafaxine
zuclopenthixol

Drug Inducers of CYP2D6 Enzyme

dexamethasone
rifampin

Drug Inhibitors of CYP2D6 Enzyme

STRONG INHIBITORS
bupropion
cinacalcet
fluoxetine
paroxetine
quinidine

MODERATE INHIBITORS
duloxetine
sertraline
terbinafine

WEAK INHIBITORS
amiodarone
cimetidine

OTHER KNOWN INHIBITORS:*

ANALGESICS
celecoxib
methadone

ANTIEMETIC/PROKINETICS
metoclopramide

ANTIHISTAMINES
chlorpheniramine
clemastine
diphenhydramine
hydroxyzine

ANTINEOPLASTICS
doxorubicin

ANTIRETROVIRAL, HIV INHIBITORS
ritonavir
indinavir

ANTITHROMBOTIC AGENTS
ticlopidine

CARDIOVASCULAR
midodrine

HISTAMINE H2 ANTAGONIST, ACID SUPPRESSANTS
ranitidine

PSYCHOTROPICS
chlorpromazine
citalopram
clomipramine
cocaine
doxepin
escitalopram
haloperidol
perphenazine
pimozide
thioridazine

*Extent of inhibition not well defined, degree of inhibition may vary.
This chart is a partial listing of drugs known to affect CYP2D6 activity based on data from:
1. http://medicine.iupui.edu/clinpharm/ddis/table.aspx
2. http://www.pharmgkb.org/gene/PA128
3. FDA-approved drug information

Table 19: Substrates of CYP3A4, CYP2C9 and CYP2C19 With a Narrow-Therapeutic Index

SUBSTRATES		
CYP3A4	**CYP2C9**	**CYP2C19**
Alfentanil	Acenocoumarol	Amitriptyline
Amiodarone	Fosphenytoin	Clopidogrel
Astemizole	Phenytoin	Imipramine
Carbamazepine	Warfarin	s-Mephenytoin
Cisapride		
Cyclosporine		
Dihydroergotamine		
Ergotamine		
Fentanyl		
Pimozide		
Quinidine		
Sirolimus		
Tacrolimus		
Terfenadine		

APPENDIX 10: 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.

Source: Tirkes T, Hollar M, Tann M, et al. Response Criteria in Oncologic Imaging: Review of Traditional and New Criteria. RadioGraphics. 2013;33:1323-41.