NCT #NCT03042611

Statistical Analysis Plan

Protocol No.: LSK-AM301

A Prospective, Randomized, Double-Blinded, Placebo-Controlled, Multinational, Multicenter, Parallel-group, Phase III Study to Evaluate the Efficacy and Safety of Apatinib plus Best Supportive Care (BSC) compared to Placebo plus BSC in Patients with Advanced or Metastatic Gastric Cancer (GC)

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History of Revision

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of covariance
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BP	Blood Pressure
BSC	Best Supportive Care
BSLN	Baseline
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CK	Creatinine Kinase
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DC	Discontinuation
DCF	Docetaxel; Cisplatin; 5-fluorouracil
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
ECF	Epirubicin; Cisplatin; 5-fluorouracil
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	EuroQol 5-Dimension 5-Level
F/U	Follow-Up
FAS	Full Analysis Set
FDA	Food and Drug Administration
GC	Gastric Cancer

GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
GIST	Gastrointestinal Stromal Tumor
Hb	Hemoglobin
HBc antibody	Hepatitis B core antibody
HBs antibody	Hepatitis B surface antibody
HBs antigen	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HFS	Hand-Foot Syndrome
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IB	Investigational Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect Model Prepeat Measurement
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NDA	New Drug Application
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD	Pharmacodynamic
PET	Positron Emission Tomograhy
PFS	Progression Free Survival
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response
PT	Prothrombin Time
PT	Preferred Term
PTT	Partial Thromboplastin Time
PVDC	Polyvinylidene Chloride
q.d.	Once a Day
QOL	Quality of Life

RBC	Red Blood Cell
RECIST	Response Evaluation Criteria for Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCRN	Screening
SD	Stable Disease
SD	Standard Deviation
SNPs	Single-Nucleotide Polymorphisms
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
Tx	Treatment
ULN	Upper Limit of Normal
USA	United States of America
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
vs	versus

1. INTRODUCTION

Gastric cancer is the 4th most common cancer world-wide and is the 4th most common cause of cancer-related death. The prevalence rate of gastric cancer is higher in Asia, South America and Eastern Europe than in Western Europe and North America.

Rivoceranib mesylate (also known as apatinib mesylate) is a novel angiogenesis inhibitor and is being developed for the treatment of advanced gastric cancer. The generic name has been now established as rivoceranib mesylate in consultation with the USAN and INN naming conventions. Rivoceranib mesylate was previously referred to by the laboratory code, YN968D1, and the nonproprietary name in China, apatinib mesylate. Rivoceranib mesylate will be manufactured as an oral tablet in 100 mg and 200 mg strengths of rivoceranib freebase. Many prior studies were conducted referring to the dose of rivoceranib as the weight of rivoceranib including the mesylate salt. In this study and in future studies, LSK will refer to rivoceranib dose strength as the weight of the rivoceranib freebase alone instead of weight of the rivoceranib mesylate salt. The freebase dosage is approximately 81% of the mesylate dosage.

This phase III study assesses the benefit of rivoceranib treatment at 700 mg/day of YN968D1 (as rivoceranib mesylate). . This dose was selected because it was the maximum dose investigated in the phase I study. This study will assess the benefit of rivoceranib plus best supportive care versus placebo plus best supportive care in regards to overall survival (OS), progression free survival (PFS), tumor response rate, disease control rate and quality of life. The target population is advanced and metastatic gastric cancer subjects who have failed at least two approved standard treatments (disease progression or intolerant to available approved drugs).

Rivoceranib is administered as a mesylate salt and was designed based on computer modeling to develop a molecule that was specific for the vascular endothelial growth factor receptor (VEGFR)-2. Rivoceranib selectively binds to and inhibits vascular endothelial growth factor receptor-2 (VEGFR-2), which is believed to be principally responsible for inhibition of VEGF-stimulated endothelial cell migration, proliferation and decreases in tumor microvascular density (MVD). Results from various laboratory tests showed that rivoceranib highly selectively inhibited protein tyrosine kinase VEGFR-2/KDR (IC_{50} about 1 nM) receptor, and rivoceranib demonstrated an anticancer effect in gastric cancer cell line (NCI-N87 cell line) implanted-nude mouse. In mice with hypodermic implantation of colorectal, liver, kidney, breast or non-small cell cancer cells, rivoceranib also demonstrated an anticancer effect. Also, a combination therapy of oxaliplatin and rivoceranib showed a high cancer cell growth inhibitory effect while having no increase in toxicity.

As a result of a phase I clinical study conducted in subjects with advanced solid tumors, rivoceranib mesylate had an MTD of 850 mg and the clinically recommended dose was 750 mg. The most common side effects were hypertension, proteinuria, and hand-foot syndrome. These side effects were mild to moderate in severity and were manageable. In terms of effectiveness, 83.8% of subjects had controlled disease; with partial response in 18.9% of subjects and stable disease in 64.9% of subjects. Out of 22 subjects with gastric-colorectal cancer who were included in the study, 18 showed controlled disease with 4 partial responses indicating a promising effect. Phase II and phase III clinical studies conducted in China showed an increase of overall survival compared to the placebo group in subjects with advanced gastric cancer. Based on the positive outcome, rivoceranib (known as apatinib in China) was approved in China for treatment of advanced gastric cancer in 2014.

Previous studies have shown clinical benefits in OS and PFS, however, there is no treatment option for patients who have failed approved standard therapies for advanced or metastatic gastric cancer. As described above, rivoceranib has shown a potential survival benefit in patients with gastric cancer; therefore, its efficacy and safety will be ascertained in this controlled and properly powered phase III study. This study will be the steppingstone to continue the clinical development of rivoceranib as a treatment agent for advanced and metastatic gastric cancer. Moreover, the data to be obtained from this study will contribute to our understanding of this disease.

This document describes the methods that will be used in summarizing and analyzing the efficacy, safety, and correlative pharmacodynamic biomarker and genetic polymorphism data that will be collected in this study. The methods for analyzing pharmacokinetic and extension period data will be addressed in separate analysis plans.

Note: For purposes of this SAP, Rivoceranib will be used as the nonproprietary name throughout the document. Apatinib was formerly used in other supporting documents, such as the protocol.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of rivoceranib administered with best supportive care (BSC) in the target population in terms of improving overall survival compared with that of placebo administered with best supportive care (BSC).

2.2 Secondary Objective

The secondary objectives of this study are as follows:

- To evaluate progression-free survival (PFS)
- To evaluate objective response rate (ORR)
- To evaluate disease control rate (DCR)
- To evaluate EORTC QLQ-C30 and EORTC QLQ-STO22
- To evaluate EQ-5D-5L
- To explore pharmacodynamic markers:
  Vascular Endothelial Growth Factor (VEGF), sVEGFR-1, sVEGFR2, and sVEGFR3
- To evaluate pharmacokinetics

Moreover, the safety of rivoceranib will be evaluated and safety measures are as follows:

- Adverse events, laboratory tests, vital signs, physical examination, 12-lead ECG, and ECOG performance status

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a prospective, randomized, double-blinded, placebo-controlled, multinational, multicenter, parallel-group, phase III study to evaluate the efficacy and safety of Rivoceranib plus Best Supportive Care (BSC)

compared to Placebo plus BSC in subjects with advanced or metastatic gastric cancer who failed two or ≥ three prior treatment regimens.

After informed consent and screening procedures, eligible subjects will be randomized in a 2:1 ratio to Rivoceranib or Placebo group. All subjects will receive best supportive care (BSC). The randomization will be stratified by the following factors: Geographic region (Asia vs. North America/Europe), Disease measurability (measurable vs. nonmeasurable), Prior ramucirumab treatment (Yes vs. No), and Treatment therapy line (3^{rd} vs. ≥ 4^{th}).

Randomized subjects will receive either the test product Rivoceranib (freebase) at 700 mg/day plus BSC or Placebo plus BSC and will be evaluated at regular site visits, which will be made every 2 weeks till the death of the subject or discontinuation of the study treatment due to disease progression, intolerable toxicity or subject's withdrawal of consent. If treatment related toxicity is detected, two steps of dose reductions (600 mg, 400 mg for Rivoceranib) are allowed during the entire study period according to the dose adjustment plan.

Tumor response and progression will be assessed every other cycle (8 weeks interval) by a local imaging facility. Subject treatment decisions will be made based on local imaging results and investigator opinion which will be entered into the case report forms. Scans will be obtained at baseline and throughout the study and will be analysed post-study by a central imaging analysis facility. Centrally imaging results will determine the subjects best tumor response and time of progression according to RECIST 1.1.

Post-treatment follow-up visit will be made at 4 weeks after the end of treatment (EOT) and then survival follow-ups will follow at 8-week intervals till the death of the subject or closure of the study.

The study data will be analysed when the required number of events (approximately 325 deaths) are observed. This is projected to occur approximately 9 months after the last subject is randomized. All subjects will be treated and/or followed after randomization until the study data analysis is performed, and then they will be monitored for survival status until death.

Subjects on treatment after analysis will be provided an option to enroll in a treatment maintenance (the Extension period) protocol if approved by country and local regulatory authorities.

3.2 Study Duration

Total study duration was designed to be approximately 18 months: 9 months of recruitment period + 9 months of treatment period. The study recruitment period extended to 21 months thus total study duration became 30 months in Protocol version 4.1 and in subsequent Protocol version 5.0. The extension period may continue beyond 30 months. The study data will be analysed when the required number of events (approximately 325 deaths) are observed. This is projected to occur approximately 9 months after the last subject is randomized. All subjects will be treated and/or followed after randomization until the study data analysis is performed, and then they will be monitored for survival status until death. Patients continuing to benefit from rivoceranib treatment, after final analysis and subsequent unblinding, will be given an option to consent to continue treatment with rivoceranib. Placebo patients will stop taking the placebo and will be monitored for survival status until death.

3.3 Administration of Investigational Product

Investigational products will be administered orally once a day, approximately 1 hour after breakfast. It is recommended that the administration time should be consistent throughout the study period (that is, the administration interval should be approximately 24 hours). The investigational product should not be taken until during the clinic visit of Day 1 of each cycle.

Subjects should take 3 tablets of 200 mg and 1 tablet of 100 mg in strength at a time. If the dose is reduced to 600 mg, 3 tablets of 200 mg in strength should be taken. If the dose is reduced further to 400 mg, only 2 tablets of 200 mg in strength should be taken at a time. If the subject vomits after swallowing the IP, the dose will not be replaced and there will be no replacement of a missed dose of IP.

3.4 Randomization

Subjects will be randomized in a 2:1 ratio to the Rivoceranib group or the Placebo group, and the randomization will be stratified according to the following factors.

1. Geographic region (Asia pacific vs. North America/Europe)
2. Disease measurability (Measurable vs. Non-measurable)
3. Prior ramucirumab treatment (Yes vs. No)
4. Treatment therapy line (3^{rd} vs. $\geq 4^{th}$)

For each subject who has provided written consent and whose eligibility is confirmed, a registration number will be assigned by the Interactive Web Response System (IWRS), and the subject will be enrolled in the study (enrollment). Detailed procedures for IWRS use will be specified in a separate document.

3.5 Japan Specific Safety Run-in

The AM104 ethnic bridging study determined that there is no statistically significant difference in Japanese ethnic population pharmacokinetics as compared to Chinese and/or Caucasian that would make it unsafe to proceed at the study starting dose. The AM104 study evaluated the pharmacokinetics of a single dose of 201 mg of Rivoceranib in 18 healthy volunteers of each of three specific ethnic populations; Japanese, Chinese and Caucasian. Initiation of enrollment in Japan included a safety run-in approach to further confirm the safety of the study starting dose in this ethnic population.

Initially, in Japan, only 6 subjects were enrolled and assigned either Rivoceranib or Placebo to investigate the safety at the same starting dose and with the same randomization/enrollment criteria as all other study subjects. The treatment assignments were not known to any study personnel with the following exceptions. During the observation period, an appropriately unblinded and separate study personnel in the study team who would perform no other study activity or duties that would jeopardize the integrity of the study, determined whether at least 3 of the first 6 subjects were assigned to Rivoceranib treatment. These specific subjects were hospitalized and monitored during the 14 days of DLT evaluation period including performing the following evaluations once on either study day 7, 8 or 9 that was not noted in the standard study schedule,

- Physical examination
- Measurement of vital signs including weight

- Assessment of ECOG performance score
- Assessment of adverse event
- Collection of concomitant medication information
- Hematology, blood chemistry, coagulation test and urinalysis

If at least 3 were assigned Rivoceranib treatment, the Rivoceranib treated subjects would be observed for a minimum of 14 days of therapy. If less than 3 subjects were randomized to Rivoceranib treatment, 3 more subjects (bringing the total to 9 subjects) could have been enrolled immediately to ensure that the DLT evaluation in Japan subjects was performed on at least 3 Rivoceranib treated subjects.

If no DLT occurred during the DLT evaluation period (at least 0/3 rivoceranib treated subjects), the study could proceed in Japan with further enrollment per protocol and the IDMC and PMDA would be notified.

If there was only 1 DLT during the DLT evaluation period (at least 1/3), another 3 subjects could have been enrolled to ensure that at least 6 Rivoceranib subjects were observed for the 14 day DLT evaluation period.

If there remained only 1 DLT during the DLT evaluation period after at least 6 Rivoceranib treated subjects were observed (at most 1/6 Rivoceranib treated subjects), the study could proceed in Japan with further enrollment per protocol and the IDMC and PMDA would be notified.

If there were 2 DLT events in the 14 day DLT evaluation period (either at most 2/3 or at least 2/6 Rivoceranib treated subjects), then the subject data (AE, SAE, DLT, etc) in EDC with randomization information would be sent to the independent contract research organization for interim analyses (AXIO Research, LLC). AXIO would merge the subject information with the randomization information for presentation to the IDMC. AXIO would schedule a teleconference to review the information with the IDMC, which would discuss recommendation regarding whether discontinue or continue enrollment with or without study design modifications. Such a study design modification could be but not limited to:

- Dose modification
- Extended safety run-in
- Request for additional safety monitoring

Then AXIO would transfer the IDMC's recommendation to LSKB and LSKG. The enrollment in Japan would temporarily stop until sponsor's decision to discontinue or continue enrollment with or without modifications after consultation with PMDA.

The notification of the outcome of the Japan Safety Run-in would also be given to each site. In addition, if a DLT occurred, a notification would be made in a timely manner to all investigators that had subjects being treated on study.

For the purposes of the Japanese safety run-in, a DLT is defined as any of the following events assessed by the Investigator as probably or possibly related to Rivoceranib that occurs during or after the initial dose on Day 1 through Day 14.

1. CTCAE Grade 4 event
2. Grade 3 febrile neutropenia (<1,000 neutrophils/mm^3)
3. Grade 3 anemia and thrombocytopenia with duration > 7 days
4. Grade 3 non-hematologic toxicity including Grade 3 nausea, vomiting and diarrhea that

continues despite optimal medical management

5. Anemia or thrombocytopenia that requires transfusion
6. When the study treatment was withheld based on the protocol 4.4 dose adjustment plan more than three day

Of note, the first 6 subjects enrolled in Japan were evaluable, were confirmed that at least 3 were administered rivoceranib and no DLT was observed in any of these subjects.

3.6 Study Scheme

Overview of study design is summarized in Figure 1.

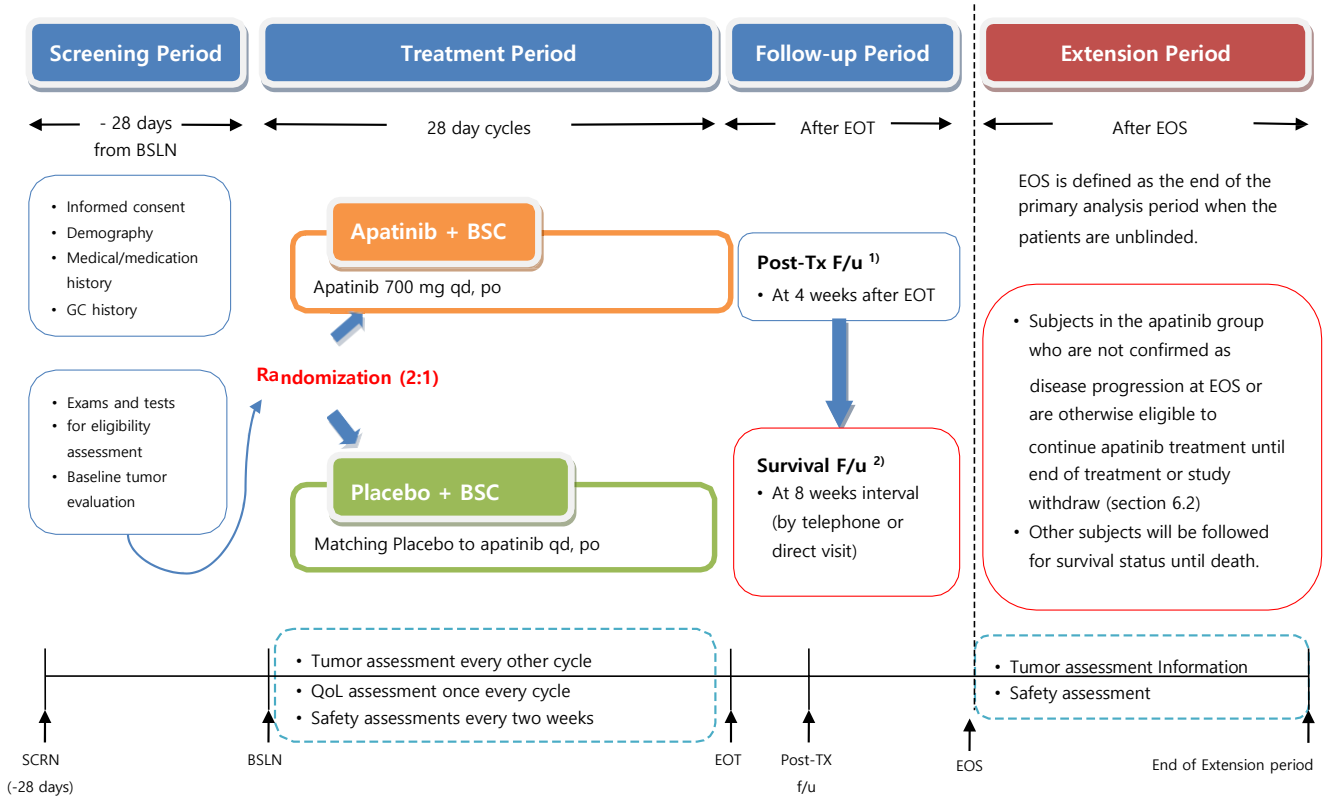


Figure 1. Study Scheme

1) Post-treatment follow-up will be done at 4 weeks (± 7 days) after the end of treatment (EOT).
2) Survival follow-up will be done at 8 weeks (± 7 days) interval after the Post-treatment follow-up visit. Survival follow-ups will continue until the death of the subject or till the study closure.

3.7 Determination of the Sample Size

[redacted]

[redacted]

4. ANALYSIS SETS

4.1 Intention-To Treat Set

ITT set consists of data from all subjects who are randomized into the study. In the ITT set, subjects will be included in the group to which they were randomized. The ITT set will be used for the primary efficacy analyses.

4.2 Safety Set

Safety set consists of data from all subjects in the ITT population who received at least one dose of Rivoceranib or placebo. In the Safety set, subjects will be included in the group based on the treatment that was received. Safety data will be analyzed by safety set.

4.3 Full Analysis Set

FAS consists of data from subjects included in ITT Set who received at least one dose of Rivoceranib or placebo. The FAS will be used for supportive efficacy analyses.

4.4 Per-Protocol Set

PPS consists of data from subjects included in FAS who completed the study per protocol without major violation such as inclusion/exclusion criteria violation and use of prohibited concomitant medication during the study. The PPS will be used for supportive efficacy analyses. Whether each subject is included in the PPS will be decided in a blinded meeting based on the protocol deviations and violations before data base lock.

5. STUDY VARIABLES AND DEFINITIONS

5.1 Efficacy Variables

Based on the definition of target and non-target lesion, response of target lesions and response of non-target lesion are defined in Table 1 and Table 2 in the RECIST1.1. Centrally imaging results will determine the subjects best tumor response and time of progression according to RECIST 1.1.

Table 1. Response Criteria of Target Lesions

Response of Target Lesions	Definition
Complete response (CR)	The disappearance of all target lesions and reduction in short axis of any nodal target lesions to < 10 mm
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameters of the target lesions, taking as a reference the baseline sum diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study.

Response of Target Lesions	Definition
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of the target lesions, taking as a 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).

Table 2. Response Criteria of Non-Target Lesions

Response of Non-Target Lesions	Definition
CR	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
non-CR/non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal upper limits
PD	Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression).

With the tumor response of target, non-target and new lesion, overall response is defined in Table 3.

Table 3. Time Point Response (subjects with target and non-target lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not evaluated	Non-PD	No	Inevaluable (NE)
PD	Any response	Yes or No	PD
Any response	PD	Yes or No	PD
Any response	Any response	Yes	PD

With the tumor response of non-target and new lesion, overall response is defined in Table 4

Table 4. Time Point Response (subjects with non-target lesions only)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not evaluated	No	Inevaluable (NE)
Unequivocal PD	Yes or No	PD
Any response	Yes	PD

The best overall response without confirmation of complete or partial response is defined as the best response across all time points. When there are more than one response, it will be selected as the best overall response according to the order of CR > PR > SD > NON-CR / NON-PD > PD > NE. The minimum duration for SD to decide best response is 6 weeks.

5.1.1 Efficacy Variables Primary Endpoint

Overall Survival (OS): Time from randomization to death. Subjects alive or lost to follow-up are censored at the date the subject was last known to be alive.

5.1.2 Efficacy Variables Secondary Endpoints

Centrally imaging results will determine the subject's best tumor response and time of progression according to RECIST 1.1. for the following endpoints. In addition, supportive tumor response and progression will be analyzed based on investigator assessment.

- Progression Free Survival (PFS): Time from randomization to either documented radiological progression (PD) or death. Subjects alive and free of progression are censored at the last tumor assessment date when alive and free of progression were known. And if there is no baseline tumor assessment data for subjects, the subjects are censored at the date of randomization.
- Objective Response Rate (ORR): Proportion of subjects with a Best Overall Response of Complete Response (CR) or Partial Response (PR).
- Disease Control Rate (DCR): Proportion of subjects with a Best Overall Response of complete response (CR) or partial response (PR), or stable disease (SD).

5.2 Pharmacodynamic Variables

Levels of vascular endothelial growth factor (VEGF), soluble VEGF receptor-1 (sVEGFR-1), sVEGFR-2, and sVEGFR-3 will be evaluated at baseline (on Cycle 1 Day 1 prior to first dose), on Day 1 (±3 days) of each subsequent treatment cycle, and at the End of Treatment/Discontinuation visit.

All subjects will be evaluated at baseline for single nucleotide polymorphisms (SNPs) in VEGFR-2 (rs1870377, rs2305948, and rs17709898) that may provide genotype information that correlates to response to VEGFR-2 inhibition therapy.

5.3 Patient Reported Outcome

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-the gastric cancer specific module (EORTC QLQ-STO22) were used to evaluate patient reported outcome.

EORTC QLQ-C30 is a 30-item core-cancer-specific questionnaire-integrating system for assessing the health-related QOL of cancer subjects participating in international clinical trials. The questionnaire incorporates 5 functional scales (physical, role, cognitive, emotional and social), 4 symptom scales (fatigue, pain, nausea/vomiting, appetite), a global QOL scale and single items for the assessment of additional systems commonly reported by cancer subjects (e.g., constipation, diarrhoea, sleep disturbance and financial). All items are scored on 4-point Likert scales, ranging from 1 ('not at all') to 4 ('very much'), with the exception of two items in the global QOL scale which use modified 7-point linear analog scales.

Table 5. Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL	QL2	2	6	29, 30	
Functional scales					
Physical functioning	PF2	5	3	1 to 5	F
Role functioning	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range=3.

For all scales, the RawScore (i.e., RS) is the mean of the component items:

RawScore = RS = $(I_1 + I_2 + \ldots + I_n) /n$

Using the RawScore, **Functional scales**:

Scale = [1- (RS – 1) / range] * 100

Symptom scales / items and **Global health status / QoL**:

Score = [(RS - 1) / range] * 100

EORTC QLQ-STO22 is a 22-item gastric cancer-specific questionnaire-integrating system for assessing the health-related QOL of gastric cancer subjects.

Table 6. Scoring the QLQ-STO22

	Scale name	Number of items	Item range	QLQ-STO22 Item numbers
Functional scales				
Body image	STOBI	1	3	19
Symptom scales				
Dyspnoea	STODYS	3	3	1-3
Pain	STOPAIN	4	3	4-7
Reflux symptoms	STORFX	3	3	8-10
Eating restrictions	STOEAT	4	3	11-13,16
Anxiety	STOANX	3	3	17,18,20
Dry mouth	STODM	1	3	14
Taste	STOTA	1	3	15
Body image	STOBI	1	3	19
Hair loss	STOHL	2/1	3	21, 22*

* Item 22 is an optional item and depends on the answer to item 21. Item 22 should only be answered and assessed if 'yes' has been answered to item 21.

For all scales, the RawScore (i.e., RS) is the mean of the component items:

RawScore = RS = $(I_1 + I_2 + \ldots + I_n) /n$

Using the RawScore, **Functional scales and Symptom scales**:

Score = [(RS - 1) / range] * 100

Only when at least half of the items for each sub-scale have been answered, RawScore of the scale will be calculated. The RawScore is defined as the average of the items that are answered from the respondent excluding the unanswered items. When less than half of the items are answered, the corresponding score is considered as missing.

5.3.1 EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire

It consists of EQ-5D-5L descriptive system and the visual analogue scale (VAS). The descriptive system comprises the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and

each dimension has 5 levels.

5.4 Patient Reported Outcome Secondary Endpoints

The following secondary endpoints will be analyzed based on patient reported outcomes.

- Global health status/quality of life score according to European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ-STO22
- Each dimension response according to EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire

5.5 Gastric Cancer History and Current Cancer Status

5.5.1 Gastric Cancer History

All gastric cancer history within 3 year prior to screening will be collected. History of gastric cancer shall include date of diagnosis, method for diagnosis, stage at initial diagnosis, location of primary tumor at diagnosis (Gastric [≥ 5 cm below GEJ] vs. GEJ), location of metastases (metastases to other organs such as lung, liver metastasis) etc.

5.5.2 Current Cancer Status

Current disease presentation (locally advanced, metastatic or local), cancer stage at screening and location of metastases will be collected.

5.6 Anti-Cancer Therapy, Surgeries and Radiotherapy

5.6.1 Prior Anti-Cancer Therapy

Any prior anti-cancer treatments used for the management of advanced or metastatic gastric cancer (e.g. anticancer chemotherapy and/or radiotherapy) will be collected. Specifically, line of therapy, best response, reason for stopping, date of progression and agent will be collected.

5.6.2 Post Anti-Cancer Therapy

Anti-cancer treatments that is used in post-treatment follow up (after end of treatment (EOT)) will also be collected. Regimen number, reason for the regimen and agent will be collected.

5.6.3 Surgeries and procedures

Cancer-related or general surgeries/procedures will be collected in the eCRF. Location and intent of surgery will be collected. Location and result of procedures and whether the result is normal/abnormal with clinically significant or not will also be collected.

Surgeries/Procedures will be classified as prior surgeries/procedures if it meets the following conditions:

- The date of procedures is prior to first administration of study drug;

Surgeries/Procedures are defined as concomitant surgeries/procedures that meet the following conditions:

- The date of procedures is on or after the first administration of study drug and on or before the date of End of Treatment (EOT);

Surgeries/Procedures are defined as post surgeries/procedures that meet the following conditions:

- The date of procedures is after the date of End of Treatment (EOT);

Note: In the above definitions of prior, concomitant and post surgeries/procedures, the surgeries/procedures may be considered as prior, concomitant and post.

In the event of partial dates, the algorithm in Section 12.3 will be followed to determine whether the surgeries/procedures are to be considered as prior / concomitant / post.

5.6.4 Radiotherapy

Body site and intent of radiotherapy and its cumulative dose will be collected. Radiotherapy will be classified as prior, concomitant and post based on check box in the eCRF.

5.7 Medical History

General medical history within 1 year prior to screening will be collected.

5.8 Prior, Concomitant and Post Medication

Any medications or therapies that the subject was taking or receiving at the time of study participation (Screening visit) shall be recorded as concomitant medications. Medications that the subject took within 28 days from signing on the ICF shall also be recorded in the eCRF.

Medication will be classified as prior medication if it meets the following conditions:

- The start and stop date are prior to first administration of study drug;

Medication is defined as concomitant medication that meets the following conditions:

- The start date is on or after the first administration of study drug and on or before the date of End of Treatment (EOT); or
- The start date is prior to the first administration of study drug, but the stop date is on or after the first administration of study drug (or the medication is listed as ongoing);

Medication is defined as post medication that meets the following conditions:

- The start date is after the date of End of Treatment (EOT);

Note: In the above definitions of prior, concomitant and post medication, a medication may be considered as prior, concomitant and post in the same time.

In the event of partial dates, the algorithm in Section 12.3 will be followed to determine whether the medication is to be considered as prior/concomitant /post.

5.9 Safety Variables

5.9.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject who has signed the informed consent form. The event need not necessarily have a causal relationship with the investigational product.

Examples of AEs include but are not limited to:

- Abnormal test findings that are clinically significant.
- Clinically significant symptoms and signs.
- Clinically significant changes in physical examination findings.
- Signs or symptoms resulting from drug overdose, misuse, or withdrawal.

Disease progression assessed by measurement of malignant lesions on imaging studies should not be reported as an AE.

5.9.2 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as AEs that have a start date on or after the first dose of the investigational product until the final subject visit or, if it has a start date before the date of the first dose of study drug, increase in severity on or after the date of the first dose of investigational product until the final subject visit. If there are partial or missing dates, the imputation algorithm in Section 11.3 will be followed to decide whether the AE is TEAE.

Adverse events collected during screening period (from the time-point of informed consent until right before the first administration of the investigational product) will be separately listed and reviewed.

5.9.3 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.[1)]
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

[1)] This does not include any of the following:

- Hospitalization or prolongation of existing hospitalization for a procedure (e.g., surgery, examination) that had been planned before the study
- Hospitalization or prolongation of existing hospitalization for follow-up observation of an already healed or improved condition
- Hospitalization or prolongation of existing hospitalization for examination or education
- Hospitalization or prolongation of existing hospitalization for non-medical reason (e.g., temporary absence of a family member)
- Admission to a hospice facility, nursing care facility, or rehabilitation facility

5.9.4 Adverse Drug Reaction (ADR)

An adverse drug reaction is defined as an AE that is considered certain, probable/likely, possible, unlikely, conditional/unclassified or unassessable/unclassifiable related to study medication.

5.9.5 Does Limiting Toxicity (DLT)

Dose Limiting Toxicity data was collected only for the subjects enrolled in Japan Run-in. Whether the DLT occurred or not (Yes/No), and any of the following event occurred will be collected:

1. CTCAE Grade 4 event
2. Grade 3 febrile neutropenia (<1,000 neutrophil/mm3)
3. Grade 3 anemia and thrombocytopenia with duration >7 days
4. Grade 3 non-hematologic toxicity including Grade 3 nausea, vomiting and diarrhea that continues despite optimal medical management
5. Anemia or thrombocytopenia that requires transfusion
6. When the study treatment was withheld based on the protocol 4.4 dose adjustment plan more than three days

5.9.6 Vital Signs

Systolic blood pressure, diastolic blood pressure, pulse, body temperature, respiratory rate, weight, height and BMI will be collected. Weight (kg) will be measured at each visit and height (cm) will be measured only at the screening visit.

5.9.7 12-Lead Electrocardiogram (ECG)

Heart rate, PR interval, QTcF, RR interval, ST segment, T-wave, Heart rate, and whether the result is normal/abnormal and clinically significant/not-significant will be collected. For Day 1 of Cycle 1 and 2, 12-lead ECG will be collected before the IP administration and approximately 4 hours after IP administration which corresponds to the time when the PK C_{max} blood is drawn.

5.9.8 Laboratory Data

- Hematology (complete blood count, CBC: white blood cell (WBC) with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, absolute neutrophil count (ANC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct)
- Blood chemistry: sodium, potassium, chloride, carbon dioxide or bicarbonate (if required), blood urea nitrogen (BUN), creatinine, glucose (fasting), total protein, albumin, calcium, amylase, lipase, phosphorous, magnesium, creatinine kinase (CK), uric acid, total bilirubin, AST, ALT, and ALP
- Serological tests: HIV antibody (if HIV antibody result is positive, HIV-1 antibody and HIV-2 antibody should be conducted), HBs antigen, HBs antibody, HBc antibody, HCV antibody
- Coagulation tests: prothrombin time expressed as either prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT or aPTT)
- Urinalysis: specific gravity, protein, glucose, occult blood, and microscopic examination if indicated
- Pregnancy test: it will be carried out only for female subjects with child-bearing potential (serum or urine).

5.9.9 Physical Examination

Any abnormal physical findings on eye, ears, nose, throat, neck, thyroid, cardiovascular system, respiratory system, gastrointestinal system or mouth, dermatologic system, extremities, musculoskeletal system,

central and peripheral nervous system, lymph nodes will be collected. Whether the finding is clinically significant will also be checked.

5.9.10 ECOG performance

ECOG performance score (0,1,2,3,4) will be collected.

Table 7. ECOG Grade

ECOG Grade	Description
0	Fully active, 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 house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

6. DISPOSITION AND PROTOCOL DEVIATIONS

6.1 Subject Disposition

Subjects in each analysis set (ITT Set, FAS, PPS and Safety Set) will be summarized with counts and *percent* by treatment group for all enrolled subjects. Reason excluded from each analysis set will be summarized with counts by treatment group. Subjects excluded from each analysis set will be listed.

The disposition of all screened subjects will be summarized by treatment group. The number of subjects who are randomized (treated/Non-treated) and the number of subjects who are completed/Withdrawn will be summarized by treatment group. The withdrawn subject will be listed.

In addition, for subjects who prematurely discontinue from the study, the reasons for withdrawn will be summarized with counts by treatment group and for the ITT set. The number of randomized subject will also be summarized by region, country and by investigator. The number of randomized subject will be summarized with counts and percent by the stratification.

The disposition tables will include the following summaries by treatment and overall:

- Analysis populations (all subjects)
- Enrollment by region, country and site (ITT population)
- Summary of randomization stratification per IWRS (ITT population)
- Study Treatment Disposition and Discontinuation (ITT population)
- Study Status, Duration of Treatment and Study Exit (ITT population).

➢ Duration of Treatment (month) = (Date of last treatment admin.– Date of first treatment admin. +1)

x 12/365.25

- Duration of Study (month)
  = Date of (End of study – Date of Randomization +1) x 12/365.25; for study discontinued/completed.
  = Date of (the last visit – Date of Randomization +1) x 12/365.25; for study ongoing.

Data will be summarized in the following tables:

- *Table. Subject Disposition – All Screened Subjects*
- *Table. Subject Population – All Enrolled Subjects*
- *Table. Enrollment by Geographic Region – ITT*
- *Table. Enrollment by Country– ITT*
- *Table. Enrollment by Site – ITT*
- *Table. Summary of Randomization Stratification – ITT*
- *Table. Duration of Treatment - ITT*

- *List. Analysis Set – ITT*
- *List. Withdrawn Subjects – ITT*

6.2 Protocol Deviations

The study team will conduct reviews of the protocol deviation and violation (PDV) data and resulting set of PPS population subjects throughout the study, adjusting the PDV criteria as seems appropriate. The PPS population subjects set will be finalized at the blind meeting (or earlier), prior to database lock.

All protocol deviations and violations data will be listed.

Data will be summarized in the following table and list.

- *Table. Major Protocol Deviation – ITT Set*
- *List. Subjects with Major Protocol Deviation – ITT Set*

7. EFFICACY EVALUATION

7.1 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized by descriptive statistics by treatment group for the ITT set. The number of subjects, mean, standard deviation, minimum and maximum will be presented for continuous data, and the number and percentage (%) of subjects will be presented for categorical data.

For the demographics, the following variables will be summarized:

- Continuous Variables: Age (years), Weight (Kg) at baseline, Height(cm), BMI(Kg/m^2) at baseline
- Categorical Variables: Sex(Male, Female), History of drug abuse (Yes, No), History of alcohol

abuse(Yes, No), Ethnicity (Hispanic of Latino, Not Hispanic or Latino), Race(American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Others), Geographic Region (Asia pacific, North America/Europe), Disease Measurability (Measurable, Nonmeasurable), Prior Ramucirumab Treatment (Yes, No), Treatment Therapy Line (3^{rd}, ≥ 4^{th})

- Age(years) = Year of consent – year of birth; If consent date is after birth date

  Year of consent – year of birth-1; If consent date is before birth date
- BMI(kg/m^2) = Weight(kg)/[height (cm)/100]^2

Data will be summarized in the following tables.

-Table. Demographic and baseline characteristics – ITT

- List. Demographic data – ITT

7.2 Cancer History and Cancer Therapy/Surgeries/Procedures/Radiotherapy

Gastric cancer history, current cancer status, anti-cancer therapy, surgeries, procedures and radiotherapy will be summarized presenting descriptive statistics by treatment group for the ITT set. For anti-cancer therapy will be coded using WHO-DDE 2017(ATC code). The number and percentage (%) of subjects will be presented based on 'Anatomical main group(level 1)' and 'Therapeutic subgroup(level 2)' by treatment group. For surgeries/procedures, the number and percentage (%) of subjects will be presented based on Preferred Term(PT) and System Organ Class(SOC) using Medical Dictionary of Regulatory Activities (MedDRA) version 19.0 or higher. For anti-cancer therapy, surgeries/procedures and radiotherapy, p-value that tests homogeneity of proportions between treatment groups (chi-square test or Fisher's exact test) will be presented.

Data will be summarized in the following tables.

-Table. Gastric Cancer History – ITT
-Table. Current Cancer Status – ITT
-Table. Prior Anti Cancer – ITT
-Table. Prior Anti Cancer Therapy by Anatomical and Therapeutic Class – ITT
-Table. Post Anti Cancer Therapy by Anatomical and Therapeutic Class – ITT
-Table. Prior Surgeries and Procedures by SOC and PT – ITT
-Table. Concomitant Surgeries and Procedures by SOC and PT – ITT
-Table. Post Surgeries and Procedures by SOC and PT – ITT
-Table. Prior Radiotherapy – ITT
-Table. Concomitant Radiotherapy – ITT
-Table. Post Radiotherapy – ITT

7.3 Medical History

Medical History will be summarized by treatment group for the ITT set. The number and percentage (%) of subjects will be presented based on Preferred Term (PT) and System Organ Class(SOC) using Medical

Dictionary of Regulatory Activities (MedDRA) version 19.0 or higher. P-value that tests homogeneity of proportions between treatment groups (chi-square test or Fisher's exact test) will be presented.

Data will be summarized in the following tables.

- *Table. Medical History by SOC and PT – ITT*

7.4 Prior and Concomitant Medications

All collected medications will be classified as Prior or Concomitant Medications according to Section 5.5, and coded by using WHO-DDE 2017(ATC code). For ITT set, the number and percentage (%) of subjects will be presented based on 'Anatomical main group (level 1)' and 'Therapeutic subgroup(level 2)' by treatment group. P-value that tests homogeneity of proportions between treatment groups (chi-square test or Fisher's exact test) will be presented

Data will be summarized in the following tables.

- *Table. Prior Medication by Anatomical and Therapeutic Class – ITT*
- *Table. Concomitant Medication by Anatomical and Therapeutic Class – ITT*
- *Table. Post Medication by Anatomical and Therapeutic Class – ITT*

7.5 Efficacy Analysis

7.5.1 Multiple Comparison Procedure on Primary and Key Secondary Endpoints

To control the family-wise error rate (FWER) on testing multiple hypotheses of interest, the fixed sequence closed testing procedure will be used. In this fixed sequence procedure, each hypothesis will be sequentially tested with two-sided 5% level only if higher level hypothesis is rejected. For this fixed sequential testing, the primary and key secondary efficacy endpoints will be tested using the ITT set. Specifically,

1. Test OS with two-sided 5% level
2. If OS is significant, test PFS (based on central review) with two-sided 5% level
3. If OS and PFS are significant, test ORR (based on central review) with two-sided 5% level

If a prior test is not statistically significant, then the subsequent analyses will be exploratory rather than confirmatory.

7.5.2 Primary Efficacy Analysis

- Overall Survival (OS): Time from randomization to death. Subjects alive or lost to follow-up are censored at the date the subject was last known to be alive.

The primary efficacy endpoint (OS) will be analyzed using ITT, FAS and PPS. The primary efficacy analysis will be conducted using the ITT set. The final analysis will be conducted when approximately 325 events are observed.

The comparison of OS between the two treatment groups will be performed with a logrank test stratified on the randomization stratification variables Geographic region (Asia vs. North America/Europe), Prior

ramucirumab treatment (Yes vs. No), and Treatment therapy line (3rd vs. ≥ 4th) at the two-sided alpha=0.05 level of significance.

In order to estimate the hazard ratio, a Cox proportional hazards regression model will be fitted with treatment group as a factor and the randomization stratification variables [Geographic region (Asia vs. North America/Europe), Disease measurability (measurable vs. nonmeasurable), Prior ramucirumab treatment (Yes vs. No), and Treatment therapy line (3rd vs. ≥ 4th)] as covariates. The hazard ratio and its 95% confidence interval will be presented.

Kaplan-Meier estimates will be calculated for each treatment group to construct the survival curve. The median overall survival and its 95% CI (based on Greenwood formula) will be presented. The primary endpoints will also be analyzed using the FAS and PPS.

Data will be summarized in the following tables and figures.

-Table. Overall Survival – ITT
-Table. Overall Survival – FAS
-Table. Overall Survival – PPS

-Figure. Kaplan Meier Plot for Overall Survival – ITT
-Figure. Kaplan Meier Plot for Overall Survival – FAS
-Figure. Kaplan Meier Plot for Overall Survival – PPS

7.5.3 Key Secondary Efficacy Analysis

The key secondary efficacy endpoints (PFS, ORR) will be analyzed using ITT, FAS and PPS. The key secondary efficacy analyses will be conducted using the ITT set.

- Progression Free Survival (PFS): Time from randomization to either documented radiological progression (determined by the central imaging analysis facility) or death from any cause. Subjects alive and free of progression are censored at the last tumor assessment date when alive and free of progression were known.
- Objective Response Rate (ORR): Percentage of subjects with a Best Overall Response (determined by the central imaging analysis facility) of Complete Response (CR) or Partial Response (PR).

PFS will be analyzed using the same statistical methods that are used in the primary efficacy analysis of OS.

ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors Geographic region (Asia vs. North America/Europe), Prior ramucirumab treatment (Yes vs. No), and Treatment therapy line (3rd vs. ≥ 4th). For the ORR, the frequency and percentage (with 95% CI) of subjects will also be provided.

Data will be summarized in the following tables and figures.

-Table. Progression Free Survival [Independent Central Review] – ITT

-Table. Progression Free Survival [Independent Central Review] – FAS
-Table. Progression Free Survival [Independent Central Review] – PPS

-Figure. Kaplan Meier Plot for Progression Free Survival [Independent Central Review] - ITT
-Figure. Kaplan Meier Plot for Progression Free Survival [Independent Central Review] - FAS
-Figure. Kaplan Meier Plot for Progression Free Survival [Independent Central Review] – PPS

-Table. Objective Response Rate [Independent Central Review] – ITT
-Table. Objective Response Rate [Independent Central Review] – FAS
-Table. Objective Response Rate [Independent Central Review] – PPS

-Table. Progression Free Survival - [Investigator Review] – ITT
-Table. Progression Free Survival - [Investigator Review] – FAS
-Table. Progression Free Survival - Investigator Review] – PPS

-Table. Objective Response Rate - [Investigator Review] – ITT
-Table. Objective Response Rate - [Investigator Review] – FAS
-Table. Objective Response Rate - [Investigator Review] – PPS

- List. Time to Event Parameters by Subjects – ITT Set
- List. Objective Response by Subject – ITT Set

7.5.4 Other Secondary Efficacy Analysis

All other secondary efficacy endpoints will be analyzed in the ITT, FAS, and PPS using two-sided test at the alpha=0.05 level of significance, with no adjustments for multiplicity.

- Disease Control Rate (DCR): Proportion of subjects with a Best Overall Response (determined by the central imaging analysis facility) of complete or partial response (CR or PR), or stable disease (SD).
- Global health status/quality of life score according to European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ-STO22.
- Each dimension response according to EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire.

For the DCR, the same statistical method that is used in ORR will be performed.

Each derived score from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ-STO22 will be summarized by descriptive statistics by treatment group for each cycle. Each derived score from EORTC QLQ-C30 and EORTC QLQ-STO22 will also be analyzed using analysis of covariance (ANCOVA) models for each cycle with the derived change from baseline score as dependent variable, treatment group and the randomization stratification variables as factors, and the baseline score of the corresponding questionnaire as a covariate. Least

squares mean difference and 95% confidence interval with corresponding p-value for comparing two treatment groups will be presented.

For EuroQol 5-Dimension 5-Level (EQ-5D-5L), the number and percentage (%) of subjects for each level of each dimension will be presented for each cycle for both treatment groups. EQ VAS data will be analyzed using analysis of covariance (ANCOVA) models for each cycle with the derived change from baseline score as dependent variable, treatment group as a factor and the randomization stratification variables, the baseline score of the corresponding questionnaire as covariates. Least squares mean difference and 95% Confidence interval with corresponding p-value for comparing two treatment groups will be presented.

Data will be summarized in the following tables.

-Table. Disease Control Rate [Independent Central Review] – ITT
-Table. Disease Control Rate [Independent Central Review] – FAS
-Table. Disease Control Rate - [Investigator Review] – ITT
-Table. Disease Control Rate - [Investigator Review] – FAS

-Table. EORTC QLQ-C30 [Parameter]] – ITT
-Table. EORTC QLQ-C30 [Parameter] - FAS
-Table. EORTC QLQ-STO22[Parameter] – ITT
-Table. EORTC QLQ-STO22 [Parameter]- FAS
-Table. EQ-5D-5L [Parameter] – ITT
-Table.EQ-5D-5L [Parameter] – FAS

- List. EORTC QLQ-C30 – ITT Set
- List. EORTC QLQ-STO22 – ITT Set
- List. EQ-5D-5L – ITT Set

7.6 Pharmacodynamic Analysis

All pharmacodynamic parameters (VEGF, sVEGFR-2, sVEGFR-2, and sVEGFR-3) will be summarized by visit (baseline, completion of each 28-day cycle and end of treatment/discontinuation) and will also be listed. Summaries will include descriptive statistics including number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).

All SNP data will be summarized with a table detailing the distribution of SNPs at baseline with the number of subjects and corresponding percentage of each polymorphism for each SNP analyzed (i.e. rs1870377, rs2305948, and rs17709898). Each SNP analyzed will also be listed for each subject.

-Table. Summary of Pharmacodynamic Factors – ITT
-Table. Summary of SNP Distribution – ITT

-List. Pharmacodynamic Factors – ITT
-List. Subject SNP Status – ITT

8. SAFETY EVALUATION

All safety evaluation is based on Safety Set and summarized by treatment group.

8.1 Extent of Exposure

To access the extent of exposure to the treatment, descriptive statistics will be presented for number of cycles, total cumulative dose (mg), duration of treatment (days), delivered dose intensity (mg/day) and relative dose intensity (RDI) by treatment group. Also, subjects with one or more dose interruptions, subjects with one or more dose adjustment and subjects off treatment will be summarized. The number of cycles will refer to all cycles started, including those discontinued or temporarily suspended.

Exposure related variables are defined as:

- The duration of treatment (days) = Date of last treatment admin.– Date of first treatment admin. +1
- Delivered Dose Intensity (mg/day) = Total dose delivered / The duration of treatment
- Relative Dose Intensity (RDI) = Delivered Dose Intensity (mg/day) / 700 mg/day

Data will be summarized in the following tables.

- Table. Treatment Exposure – Safety Set

- List. Drug Concentration Data – Safety Set
- List. Subjects with Dose Adjustment – Safety Set

8.2 Adverse Events

AEs will be coded by Preferred Term (PT) and System Organ Class(SOC) using version 19.0 or newer of Medical Dictionary of Regulatory Activities (MedDRA). All AE tables will reflect only TEAEs defined in 5.6.2. Adverse events severity will be classified according to NCI-CTCAE (version 4.03). Adverse events that have relationship with investigational product such as certain, probable/likely, possible, conditional/unclassified or unassessable/unclassifiable will be defined as adverse drug reaction (ADRs).

8.2.1 Overall Summary of Adverse Events

The number of subjects, incidence rate with its 95% CI and number of events will be presented for TEAEs, adverse drug reaction (ADR) and serious adverse event by treatment group during the study. Chi-square test or Fisher's exact test will be used for comparison of AE incidence between groups.

Data will be summarized in the following tables.

- Table. Overall Summary of TEAEs – Safety Set
- Table. Overall Summary of Serious TEAEs – Safety Set
- Table. Overall Summary of ADRs – Safety Set
- Table. Overall Summary of Serious ADRs – Safety Set

8.2.2 Display of Adverse Events

All TEAEs and ADR will be presented according to standardized SOC and PT. The following conventions will be used in summarizing AEs:

- For subject incidence summaries, a subject will be counted only once within each SOC and within each PT.
- Summaries by NCI-CTCAE grade – if a subject reports more than 1 AE within an SOC and/or PT, the AE will the highest severity within each SOC and within each PT will be included.
- When the number of events is calculated, more than 1 AE counted as different events

Data will be summarized in the following tables and listings.

- Table. Incidence of TEAEs by SOC and PT – Safety Set
- Table. Incidence of ADRs by SOC and PT – Safety Set
- Table. Incidence of TEAEs by the Worst NCI-CTC Grade, SOC and PT [Rivoceranib + BSC] – Safety Set
- Table. Incidence of TEAEs by the Worst NCI-CTC Grade, SOC and PT [Placebo + BSC] – Safety Set
- Table. Number of TEAEs by NCI-CTCAE, SOC and PT [Rivoceranib + BSC] – Safety Set
- Table. Number of TEAEs by NCI-CTCAE, SOC and PT [Placebo + BSC] – Safety Set
- Table. Incidence of ADRs by the Worst NCI-CTC Grade, SOC and PT [Rivoceranib + BSC] – Safety Set
- Table. Incidence of ADRs by the Worst NCI-CTC Grade, SOC and PT [Placebo + BSC] – Safety Set
- Table. Number of ADRs by NCI-CTCAE, SOC and PT [Rivoceranib + BSC] – Safety Set
- Table. Number of ADRs by NCI-CTCAE, SOC and PT [Placebo + BSC] – Safety Set

- List. Subjects with TEAEs – Safety Set

8.2.3 Death and Serious Adverse Events and Other Significant Adverse Events

For Serious adverse events (SAEs, Sec 5.6.3), AEs leading to IP discontinuation and AEs leading to death, separate listings and summaries of subject counts and percents together with the number of events will be presented by treatment group and by SOC and PT. Also, subjects who died and primary reason of death will be summarized with counts and percents by treatment group.

Data will be summarized in the following tables and lists.

- Table. Incidence of Serious TEAEs by SOC and PT – Safety Set
- Table. Incidence of Serious ADRs by SOC and PT – Safety Set
- Table. Incidence of TEAEs Leading to IP Discontinuation by SOC and PT – Safety Set

- Table. Incidence of ADRs Leading to IP Discontinuation by SOC and PT – Safety Set
- Table. Incidence of TEAEs Leading to IP Dose Reduction/Interruption by SOC and PT – Safety Set
- Table. Incidence of ADRs Leading to IP Dose Reduction/Interruption by SOC and PT – Safety Set
- Table. Incidence of TEAEs Leading to Fatal Outcome by SOC and PT – Safety Set
- Table. Incidence of ADRs Leading to Fatal Outcome by SOC and PT – Safety Set
- Table. Death Summary – Safety Set- List. Subjects with Serious TEAEs – Safety Set

- List. Subjects with Serious TEAEs – Safety Set
- List. Subjects with TEAEs Leading to IP Discontinuation – Safety Set
- List. Subjects with TEAEs Leading to IP Dose Reduction/Interruption – Safety Set
- List. Subjects with TEAEs Leading to Fatal – Safety Set

8.2.4 Dose Limiting Toxicity (DLT)

Dose Limiting Toxicity data (Sec 5.6.5) will be collected only for the subjects enrolled in Japan Run-in. The incidence of DLT will be summarized and relevant subjects will be listed.

- Table. Incidence of DLT in Japan Run-in – Safety Set
- List. Subjects with DLT in Japan Run-in – Safety Set

8.3 Clinical Laboratory Evaluation

Laboratory data will be classified according to CTC Grade (NCI-CTCAE version 4.03). A shift table from baseline to worst NCI-CTC grade will be presented.

- Table. Shift from Baseline of Hematology Tests by Worst NCI-CTC Grade: Rivoceranib + BSC [Parameter] – Safety Set
- Table. Shift from Baseline of Hematology Tests by Worst NCI-CTC Grade: Placebo + BSC [Parameter] – Safety Set
- Table. Shift from Baseline of Blood Chemistry Tests – serum electrolyte by Worst NCI-CTC Grade: Rivoceranib + BSC [Parameter] – Safety Set
- Table. Shift from Baseline of Blood Chemistry Tests – serum electrolyte by Worst NCI-CTC Grade: Placebo + BSC [Parameter] – Safety Set
- Table. Shift from Baseline of Blood Chemistry Tests – liver enzymes by Worst NCI-CTC Grade: Rivoceranib + BSC [Parameter] – Safety Set
- Table. Shift from Baseline of Blood Chemistry Tests – liver enzymes by Worst NCI-CTC Grade: Placebo + BSC [Parameter] – Safety Set
- Table. Shift from Baseline of Blood Chemistry Tests – others by Worst NCI-CTC Grade: Rivoceranib + BSC [Parameter] – Safety Set
- Table. Shift from Baseline of Blood Chemistry Tests – others by Worst NCI-CTC Grade: Placebo + BSC [Parameter] – Safety Set

- Table. Shift from Baseline of Coagulation Tests by Worst NCI-CTC Grade: Rivoceranib + BSC [Parameter] – Safety Set
- Table. Shift from Baseline of Coagulation Tests by Worst NCI-CTC Grade: Placebo + BSC [Parameter] – Safety Set

To investigate a normal/abnormal shift from baseline by visit, results will be classified as Normal, Abnormal NCS, or Abnormal CS and presented with a shift table. Subjects who were ‘Normal’ or ‘Abnormal - not clinically significant (NCS)’ at baseline but shifted to ‘Abnormal - clinically significant (CS)’ will be summarized in the following tables and listings. Significant shift from baseline will be tested using McNemar’s or Bowker’s test.

- Table. Shift from Baseline of Hematology Tests [Parameter] – Safety Set
- Table. Shift from Baseline of Blood Chemistry Tests – serum electrolyte [Parameter] – Safety Set
- Table. Shift from Baseline of Blood Chemistry Tests – liver enzymes [Parameter] – Safety Set
- Table. Shift from Baseline of Blood Chemistry Tests – others [Parameter] – Safety Set

- Table. Shift from Baseline of Coagulation Tests [Parameter] – Safety Set

- Table. Shift from Baseline of Urinalysis Tests [Parameter] – Safety Set
- List. Listing of individual laboratory measurements – Safety Set
- List. Subjects Shifting from Normal or NCS at Baseline to CS at Post-treatment on Laboratory – Safety Set

8.4 Chest X-ray and Pregnancy Test

Data for Chest X-ray and Pregnancy Test will be collected whenever there is clinical indication. Clinically significant result of Chest X-ray and positive result of Pregnancy Test will be presented in the following lists.

- List. Clinically Significant Chest X-ray – Safety Set
- List. Positive Pregnancy Test – Safety Set

8.5 Other Safety Measures

8.5.1 Vital Signs

Vital Sign parameters (Systolic Blood Pressure, Diastolic Blood Pressure, Pulse, Body Temperature, Respiratory Rate, and Weight) and the change from baseline at each scheduled visit will be summarized with descriptive statistics by visit and treatment group.

Data will be summarized in the following table.

- Table. Vital Signs [Parameter] – Safety Set

8.5.2 Physical Examination

Subjects with at least once clinically significant abnormal result at all time points after first IP administration on physical examination will be summarized by treatment group. Clinically significant result of physical examination will be listed.

Data will be summarized in the following table and list.

- Table. Clinically Significant Physical Examination – Safety Set
- List. Subjects with Clinically Significant Abnormal on Physical Examination – Safety Set

8.5.3 12-lead Electrocardiogram

Values for ECG parameters (Heart rate, PR interval, QTcF and RR Interval) and the change from baseline will be summarized with descriptive statistics by time point and treatment group. The ECG result will be presented in shift tables (Normal, Abnormal NCS, or Abnormal CS) from baseline to each scheduled time point by time point and treatment group. Significant shift from baseline will be tested using McNemar's test.

Data will be summarized in the following tables and list.

- Table. 12-lead Electrocardiogram [Parameter] – Safety Set
- Table. Shift from baseline on 12-lead ECG – Safety Set
- List. Subjects Shifting from Normal or NCS at baseline to CS at Post-Treatment on 12-lead ECG – Safety Set

8.5.4 ECOG performance

ECOG performance grade (0,1,2,3,4) will be presented in shift tables from baseline to each scheduled visit by visit and treatment group. Significant shift from baseline will be tested using Bowker's test.

Data will be summarized in the following table.

- Table. Shift Table on ECOG grade – Safety Set

9. SUBGROUP ANALYSIS

Subgroup analyses will be conducted on randomization stratification factors. In the event of any randomization errors, the correct classification of the factor will be used.;

1. Geographic region (Asia vs. North America/Europe)
2. Disease measurability (Measurable vs. Non-measurable)
3. Prior ramucirumab treatment (Yes vs. No)
4. Treatment therapy line (3^{rd} vs. $\geq 4^{th}$)

In addition, a subgroup analysis will also be conducted for treatment therapy line comparing 3^{rd} vs 4^{th} vs. 5^{th}. The 5^{th} line subjects will be identified based on recorded prior lines of therapy as this was not a stratification factor.

The analysis for the efficacy endpoints OS, PFS, ORR, DCR using ITT population will be repeated for each subgroup. Descriptive statistics by visit for the efficacy endpoint will also be produced by subgroup. Note that subgroup analysis will be performed if there are sufficient subjects within a subgroup for statistical analysis. Otherwise, only descriptive statistics will be displayed.

The study has been sized to provide adequate power for the primary analysis. The subgroup analyses may not necessarily reach statistical significance at the 5% level. P-values and 95% confidence intervals will be provided but will not be considered inferential. However, a consistency of treatment effect is expected across the primary and all subgroup analyses. Subgroup analyses are mainly to demonstrate trend and assess internal consistency of any treatment benefit and/or safety signal. Only the analyses that provide meaningful information will be presented for the CSR.

Additional subgroup analyses will be performed to assess the consistency of treatment benefit per the primary outcome of overall survival. A forest plot displaying the hazard ratio and its 95% confidence interval will be generated for all the subgroups, including the four stratification groups mentioned above:

1. Treatment therapy line (3^{rd} vs. 4^{th} vs. 5^{th})
2. Age category (<65 vs. $\geq$ 65)
3. ECOG status (0 vs. 1 at baseline)
4. Race (white, Asian, black, and others)
5. Sex (male vs. female)
6. Previous gastrectomy (Yes vs. No)
7. Number of organs with metastases (<2 vs. $\geq$ 2)
8. Liver metastases (Yes vs. No)

Data will be summarized in the following tables.

-Table. Overall Survival [Asia] – ITT
-Table. Overall Survival [North America/Europe] – ITT
-Table. Overall Survival [Measurable] – ITT
-Table. Overall Survival [Non-measurable] – ITT
-Table. Overall Survival [Prior ramucirumab] – ITT
-Table. Overall Survival [No prior ramucirumab] – ITT
-Table. Overall Survival [3rd line therapy] – ITT
-Table. Overall Survival [≥ 4th line therapy] – ITT
-Table. Overall Survival [4th line therapy] – ITT
-Table. Overall Survival [5th line therapy] – ITT
-Table. Overall Survival [< 65 ages] – ITT
-Table. Overall Survival [≥ 65 ages] – ITT
-Table. Overall Survival [ECOG status at baseline: 0] – ITT
-Table. Overall Survival [ECOG status at baseline: 1] – ITT
-Table. Overall Survival [White] – ITT
-Table. Overall Survival [Asian] – ITT
-Table. Overall Survival [Black] – ITT
-Table. Overall Survival [Others] – ITT
-Table. Overall Survival [Male] – ITT
-Table. Overall Survival [Female] – ITT
-Table. Overall Survival [Previous gastrectomy] – ITT
-Table. Overall Survival [Non-previous gastrectomy] – ITT
-Table. Overall Survival [Organs with metastases: <2] – ITT
-Table. Overall Survival [Organs with metastases: ≥2] – ITT
-Table. Overall Survival [Liver metastases] – ITT
-Table. Overall Survival [Non-liver metastases] – ITT

-Table. Progression Free Survival [Asia] – ITT
-Table. Progression Free Survival [North America/Europe] – ITT
-Table. Progression Free Survival [Measurable] – ITT
-Table. Progression Free Survival [Non-measurable] – ITT
-Table. Progression Free Survival [Prior ramucirumab] – ITT
-Table. Progression Free Survival [No prior ramucirumab] – ITT
-Table. Progression Free Survival [3rd line therapy] – ITT
-Table. Progression Free Survival [≥ 4th line therapy] – ITT
-Table. Progression Free Survival [4th line therapy] – ITT
-Table. Progression Free Survival [5th line therapy] – ITT

-Table. Progression Free Survival [< 65 ages] – ITT

-Table. Progression Free Survival [≥ 65 ages] – ITT

-Table. Progression Free Survival [ECOG status at baseline: 0] – ITT
-Table. Progression Free Survival [ECOG status at baseline: 1] – ITT
-Table. Progression Free Survival [White] – ITT
-Table. Progression Free Survival [Asian] – ITT
-Table. Progression Free Survival [Black] – ITT
-Table. Progression Free Survival [Others] – ITT
-Table. Progression Free Survival [Male] – ITT
-Table. Progression Free Survival [Female] – ITT
-Table. Progression Free Survival [Previous gastrectomy] – ITT
-Table. Progression Free Survival [Non-previous gastrectomy] – ITT
-Table. Progression Free Survival [Organs with metastases: <2] – ITT

-Table. Progression Free Survival [Organs with metastases: ≥2] – ITT

-Table. Progression Free Survival [Liver metastases] – ITT
-Table. Progression Free Survival [Non-liver metastases] – ITT

-Table. Objective Response Rate [Asia] – ITT
-Table. Objective Response Rate [North America/Europe] – ITT
-Table. Objective Response Rate [Measurable] – ITT
-Table. Objective Response Rate [Non-measurable] – ITT
-Table. Objective Response Rate [Prior ramucirumab] – ITT
-Table. Objective Response Rate [No prior ramucirumab] – ITT
-Table. Objective Response Rate [3rd line therapy] – ITT

-Table. Objective Response Rate [≥ 4th line therapy] – ITT

-Table. Objective Response Rate vival [4th line therapy] – ITT
-Table. Objective Response Rate [5th line therapy] – ITT
-Table Objective Response Rate [< 65 ages] – ITT

-Table. Objective Response Rate [≥ 65 ages] – ITT

-Table. Objective Response Rate [ECOG status at baseline: 0] – ITT
-Table. Objective Response Rate [ECOG status at baseline: 1] – ITT
-Table. Objective Response Rate [White] – ITT
-Table. Objective Response Rate [Asian] – ITT
-Table. Objective Response Rate [Black] – ITT
-Table. Objective Response Rate [Others] – ITT
-Table. Objective Response Rate [Male] – ITT
-Table. Objective Response Rate [Female] – ITT
-Table. Objective Response Rate [Previous gastrectomy] – ITT
-Table. Objective Response Rate [Non-previous gastrectomy] – ITT

-Table. Objective Response Rate [Organs with metastases: <2] – ITT

-Table. Objective Response Rate [Organs with metastases: ≥2] – ITT

-Table. Objective Response Rate [Liver metastases] – ITT

-Table. Objective Response Rate [Non-liver metastases] – ITT

-Table. Disease Control Rate [Asia] – ITT

-Table. Disease Control Rate [North America/Europe] – ITT

-Table. Disease Control Rate [Measurable] – ITT

-Table. Disease Control Rate [Non-measurable] – ITT

-Table. Disease Control Rate [Prior ramucirumab] – ITT

-Table. Disease Control Rate [No prior ramucirumab] – ITT

-Table. Disease Control Rate [3rd line therapy] – ITT

-Table. Disease Control Rate [≥ 4th line therapy] – ITT

-Table. Disease Control Rate [4th line therapy] – ITT

-Table. Disease Control Rate [5th line therapy] – ITT

-Table. Disease Control Rate [< 65 ages] – ITT

-Table. Disease Control Rate [≥ 65 ages] – ITT

-Table. Disease Control Rate [ECOG status at baseline: 0] – ITT

-Table. Disease Control Rate [ECOG status at baseline: 1] – ITT

-Table. Disease Control Rate [White] – ITT

-Table. Disease Control Rate [Asian] – ITT

-Table. Disease Control Rate [Black] – ITT

-Table. Disease Control Rate [Others] – ITT

-Table. Disease Control Rate [Male] – ITT

-Table. Disease Control Rate [Female] – ITT

-Table. Disease Control Rate [Previous gastrectomy] – ITT

-Table. Disease Control Rate [Non-previous gastrectomy] – ITT

-Table. Disease Control Rate [Organs with metastases: <2] – ITT

-Table. Disease Control Rate [Organs with metastases: ≥2] – ITT

-Table. Disease Control Rate [Liver metastases] – ITT

-Table. Disease Control Rate [Non-liver metastases] – ITT

-Figure. Forest plot of Hazard Ratio for all subgroups – ITT

10. GENERAL PRESENTATION OF SUMMARIES AND ANALYSES

10.1 Significance level

Unless otherwise specified, all statistical tests will be 2-sided hypothesis tests performed at the 5% level of

significance and all confidence intervals will be 2-sided 95% confidence intervals.

10.2 Summary Statistics

Summary statistics for continuous variables/endpoints will be presented with number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Summary statistics for categorical variables/endpoints will be presented with counts (n) and percents. Unless otherwise specified, denominator of percentage is number of subjects included in the analysis set by each group.

10.3 Decimals

Mean, standard deviation, median, minimum, maximum for descriptive statistics of continuous data, and percentage for categorical data will be presented down to 2 decimal places. P-values will be reporter to 4 decimal places. If the calculated p-value is below 0.0001, it will be presented as '<0.0001'.

Results for clinical laboratory tests and vital signs will be presented to significant digits, in other words, rounded to the maximum decimal places for each item.

10.4 Statistical Analysis Methods

For a between-group comparison of categorical data, a chi-square test will be basically used and when more than 20% of the table cells have expected frequencies that are less than 5, Fisher's exact test will be presented. For confidence intervals of proportion of categorical data, if more than 20% of the table cells have expected frequencies that are less than 5, then exact 95% CIs will be calculated, otherwise approximate 95% CIs will be calculated.

10.5 Baseline

Baseline is defined as the value at Cycle 1 Day 1, or the last value observed prior to randomization if this is not available.

10.6 Study Period and Visit Window Definitions

Unless otherwise specified, data for regular scheduled visits will be summarized.

Table 8. Visit Window

Visit Name	Actual Time Point	Visit Window
Screening	~ -Week 2	-
Cycle 1 Day 1	Day 1	-
Cycle 1 Day 15	Day 15	±3 days
…		
Cycle Z Day 1	Day (28×Z + 1)	±3 days
Cycle Z Day 15	Day (28×Z + 15)	±3 days
End of Treatment (EOT)	-	±7 days
Post Treatment Follow-Up	EOT + 28 days	±7 days
Survival Follow-Up	Every 8 weeks after Post-Tx F/U	±7 days

10.7 Software for Statistical Analysis

SAS® Version 9.4 or higher (SAS institute, Cary, NC, USA)

11. DATA HANDLING COVENTIONS

11.1 Handling of Missing Data

11.1.1 Missing Value of Efficacy Variables

If any value is missing at any time point or a subject was withdrawn prior to study completion so that there are no data, they will be handled as missing without imputation.

11.1.2 Missing Value of Safety Variables

For safety endpoints, observed data will be used for analysis without imputation of missing values.

11.2 Repeated or Unscheduled Assessments

In case there are measurements from an unscheduled visit after the first dose of the investigational product, measurements at scheduled and unscheduled visit are chronologically presented in the subject list whereas summary of descriptive statistic by time point will only include measurements at scheduled visits.

11.3 Handling of Incomplete Date

For AE data, in case day or month is omitted from the start date, only collected date units will be used without any imputation of date.

When the entire start date is missing or the format of the collected AE date does not allow for comparison, the AE will be assumed to be TEAE.

For surgeries/procedures, in case day or month is omitted from the date thus collected as ‘UK’, only collected date units will be used without any imputation of date. When the entire date is missing or the format of the collected date does not allow for comparison with the first IP administration date, the surgeries/procedures are assumed to being used prior to the first dose administration date of the investigational product. When the format of the collected date does not allow for comparison with the EOT date, the surgeries/procedures are assumed to being used on or before the EOT date.

For medication, in case day or month is omitted from the start or end date thus collected as ‘UK’, only collected date units will be used without any imputation of date. When the entire start date is missing or the format of the collected start date does not allow for comparison with the first IP administration date, the medication is assumed to being used prior to the first dose administration date of the investigational product. When the format of the collected start date does not allow for comparison with the EOT date, the medication is assumed to being used on or before the EOT date. In case end date is missing or format of the collected end date does not allow for comparison, medications assumed to be ‘ongoing’.

12. INDEPENDENT DATA MONITORING COMMITTEE (IDMC) AND INTERIM ANALYSIS

12.1 IDMC

Independent data monitoring committee (IDMC) is composed of 3 members (2 clinicians and 1 statistician) who are fully independent of the entity conducting the trial. The IDMC should comply with IDMC charter in the ICH GCP guideline.

The IDMC will meet at least once prior to trial initiation (organizational meeting) and then at least three additional times at specific milestones (one for the formal interim analysis and two for the safety review) in the trial. The detailed schedule and purpose of the IDMC meetings is described in IDMC charter.

For the formal interim analysis, the IDMC will convene when approximately 163 events are observed to review unblinded results of the interim analysis. The IDMC can convene when unexpected adverse drug reaction with a Grade 3 or more (based on NCI-CTCAE 4.03) are observed. The IDMC can also convene, if necessary, to ensure appropriate review of the Japan specific safety run-in (Sec 3.5).

12.2 Interim Analysis and Stopping Rules

The interim analysis for futility will be conducted with collected clinical data when approximately 163 (approximately 50% of the required 325 events) events are observed. The independent contract research organization for the interim analysis (AXIO Research, LLC) will conduct all the interim analysis for the study. All planned study procedures such as subject enrollment, treatment and follow-up visit should be performed regardless of the interim analysis. If it is necessary to change the timing of the interim analysis, in consultations with sponsor, the IDMC can change interim analysis time and its corresponding statistical criteria for early termination.

The interim analysis for futility will assess the primary (OS) and key secondary (PFS, ORR) efficacy endpoints using the statistical methods planned for the final analysis but only for ITT population. The interim analysis for futility and two safety reviews will assess adverse events and safety endpoints. The IDMC will review the results of the interim analysis and recommend to the sponsor whether or not to terminate the trial for futility. Final decision regarding study termination will be made by the sponsor.

The IDMC and independent statisticians involved in the interim analysis should keep the interim analysis result completely confidential. The results of the interim analysis should be kept unknown to all staff involved in the conduct of the trial. If early termination is decided, the IDMC delivers the interim analysis report to the sponsor after the official unblinding procedure.

Early termination will be considered if the interim analysis is futile, that is when the calculated conditional power based on primary efficacy endpoint, overall survival (OS), is less than 0.2. The main/official futility analysis will assume future data is distributed as the current data to calculate conditional power (Pepe-Anderson-Betensky test). For additional sensitivity check, conditional power will be calculated assuming future data are distributed according to the alternative hypothesis, specifically hypothesized effect of HR=0.72 (Lan-Simon-Halperin test).

Early stopping for futility interim analysis does not inflate the Type-I error, thus Type I-error adjustment is not needed.

13. CHANGE FROM PROTOCOL

Protocol v5.0 Location(s)	SAP Location(s)	Protocol v5.0 Language	SAP Language Changed from Protocol v5.0	Reason of Change
Section. 8.1.1 p.73	Section 3.7.1 p.15	"Where HR (hazard ratio) is the ratio of median overall survival of Placebo and Rivoceranib* group."	"where HR ~~(hazard ratio) is the ratio of median overall survival of~~ denotes the hazard ratio for Rivoceranib group relative to Placebo group."	Clarify language in the protocol.
Section 8.1.3 p.74	Section 3.7.3 p.16	"325 events (413 subjects) are needed."	"a total of 325 events (413 subjects) are needed to provide approximately 80% power for Overall Survival."	Clarify language in the protocol.
Section 8.3.2 p.75	Section 4.1 Section 4.2 Section 4.3 Section 4.4 p.17	"ITT set consists of data from all subjects who are randomized." "The analysis for primary endpoint, OS and the secondary endpoints of PFS and ORR will be conducted in the ITT set." "Safety set consists of data from all subjects who received at least one dose of Rivoceranib or placebo." "The FAS will be used for all efficacy analyses." "The PPS will be used for all efficacy analyses."	"ITT set consists of data from all subjects who are randomized into the study." "~~The analysis~~ The ITT set will be used for the primary efficacy analyses ~~endpoint, OS and the secondary endpoints of PFS and ORR will be conducted in the ITT set~~." "Safety set consists of data from all subjects in the ITT population who received at least one dose of Rivoceranib or placebo." "The FAS will be used for ~~all~~ supportive efficacy analyses." "The PPS will be used for ~~all~~ supportive efficacy analyses."	Clarification that ITT set will be used for the primary efficacy analyses, and FAS and PPS will be used for supportive efficacy analyses.

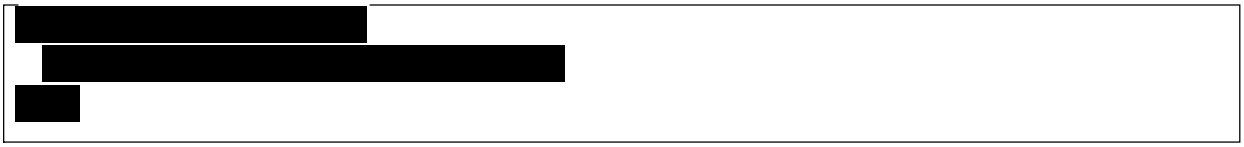
Protocol v5.0 Location(s)	SAP Location(s)	Protocol v5.0 Language	SAP Language Changed from Protocol v5.0	Reason of Change
Appendix 2: Table 3 p.91	Section 5.1 Table 4 Table 5 p.18	Table title: Time Point Response	Table title: Time Point Response (subjects with target and non-target lesion) Added table 5: Time Point Response (subjects with non-target lesion only)	Clarified on the original table and added a table to define response for subjects with non-target lesion only.
Section 8.2.1 p.74 Section 8.3.4 p.76	Section 5.1.1 p.19 Section 7.5.2 p.29	"Overall Survival (OS): Time from randomization to death. Subjects alive or lost to follow-up at the end of study (EOS) are censored."	"Overall Survival (OS): Time from randomization to death. Subjects alive or lost to follow-up at ~~the end of study (EOS)~~ analysis cut-off point are censored at the date the subject was last known to be alive."	Clarified overall survival censoring.
Section 8.2.2 p.74 Section 8.3.5 p.76	Section 5.1.2 p.19 Section 7.5.3 p.30	"Subjects alive and free of progression at the end of study (EOS) are censored."	"Subjects alive and free of progression ~~at the end of study (EOS)~~ are censored at the last tumor assessment date when alive and free of progression were known."	Clarified progression free survival censoring.
Section 8.3.5 p.76	Section 5.1.2 p.19	"Progression Free Survival (PFS): Time from randomization to either radiological progression (determined by the central imaging analysis facility) or death from any cause."	Centrally imaging results will determine the subject's best tumor response and time of progression according to RECIST 1.1. for PFS, ORR and DCR. In addition, supportive tumor response and progression will be analyzed based on investigator assessment.	Added supportive tumor response and progression analyses based on investigator assessment.
Section 8.3.4 p.76	Section 7.5.2 p.29	"The comparison of OS between the two treatment groups will be performed with a stratified log-rank	"The comparison of OS between the two treatment groups will be performed with a log-rank test stratified on the randomization stratification variables	Due to the occurrence of several very small strata for non-measurable subjects, it is not meaningful to conduct

Protocol v5.0 Location(s)	SAP Location(s)	Protocol v5.0 Language	SAP Language Changed from Protocol v5.0	Reason of Change
		test at the two-sided alpha=0.05 level of significance."	[Geographic region (Asia vs. North America/Europe), Prior ramucirumab treatment (Yes vs. No), and Treatment therapy line (3rd vs. ≥ 4th)] at the two-sided alpha=0.05 level of significance."	stratified analyses using all four randomization stratification variables. The measurable vs. non-measurable stratification criteria will not be utilized in all stratified analyses.
Section 8.3.4 p.77	Section 7.5.2 p.29-30	"For the ORR (CR or PR), …Response in both treatment groups will be compared with the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors."	"ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors Geographic region (Asia vs. North America/Europe), Prior ramucirumab treatment (Yes vs. No), and Treatment therapy line (3rd vs. ≥ 4th)."	Due to the occurrence of several very small strata for non-measurable subjects, it is not meaningful to conduct stratified analyses using all four randomization stratification variables. The measurable vs. non-measurable stratification criteria will not be utilized in all stratified analyses.
Section 8.3.4 p.82	Section 5.1.2 p.19	Entire table: Table 8. PFS censoring rule	Entire table: ~~Table 8. PFS censoring rule.~~ "Subjects alive and free of progression are censored at the last tumor assessment date when alive and free of progression were known."	Scenarios in Table 8 in the protocol is redundant and not entirely accurate, so the entire table is removed and replaced by the censoring guideline described in this SAP. Specifically, death for any cause should always be a PFS event.

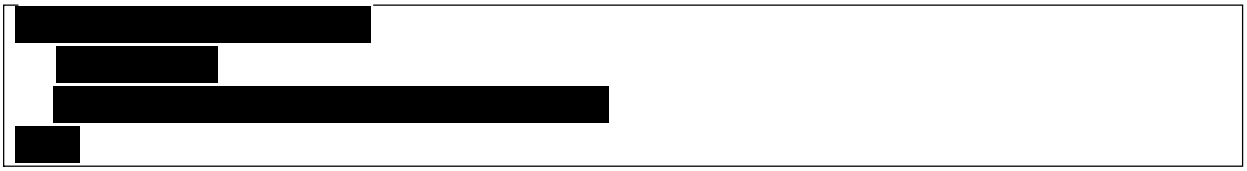
* Note: For purposes of this SAP, Rivoceranib will be used as the nonproprietary name throughout the document. Apatinib was formerly used in the protocol. In addition, grammatical and typographical changes are not included in the table.

14. SAS PROCEDURE FOR TESTING

14.1 Test of Categorical Variable for Comparison of Treatment Groups



14.2 Test for shift from baseline to post-baseline within treatment group

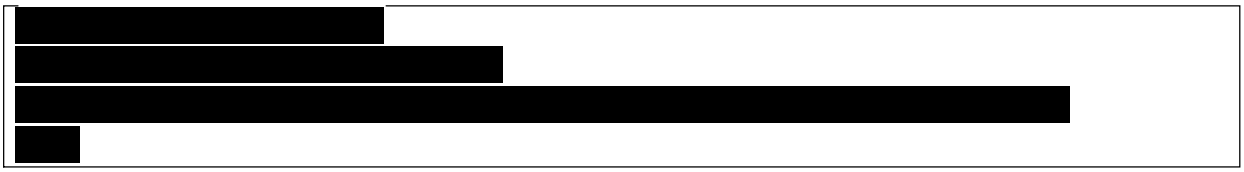


14.3 Cochran-Mantel-Haenszel test

14.4 Logrank test and Kaplan-Meier estimates

14.5 Stratified Logrank test

14.6 Cox proportional hazard regression model



14.7 Analysis of Covariance (ANCOVA)

[redacted]

15. REFERENCES

[1] Li J, Qin S, Xu J, et al. Randomized, double-blind, placebo-controlled Phase III trial of Apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol. 2016;Feb 16. pii: JCO635995.

Appendix.

Appendix 1. LIST OF TABLES, LISTINGS AND FIGURES
Appendix 1.1. Mock-up Tables
Appendix 1.2. Mock-up Figures
Appendix 1.3. Mock-up Listings