NCT #NCT03042611

CLINICAL STUDY PROTOCOL

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)

Protocol No.	LSK-AM301
Version No.	5.0
Version date	20181116
Sponsor	LSK BioPartners, Inc. 8 East Broadway, Suite 611, Salt Lake City, Utah, USA 84111
Sponsor Medical Monitor	[redacted] Phone: [redacted] Email: [redacted]
EudraCT No.	2016-003984-20
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NCT No.	NCT03042611

CONFIDENTIAL

PROTOCOL APPROVAL PAGE

PROTOCOL TITLE: 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)

PROTOCOL NO: LSK-AM301

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from LSK BioPartners, Inc.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

Name/Address of the Investigational Site _____

The following LSK BioPartners, Inc. representative is authorized to sign the protocol and any amendments:

[redacted] 26-NOV-2018

[redacted] 2018-11-26

Date (yyyy-mm-dd)

PROTOCOL REVISION HISTORY

Version	Date	Comment
1.0	13 JUN 2016	Initial Release for Regulatory Authority Review and Scientific Input – Not approved for or implemented for patient treatment.
2.0	28 OCT 2016	Protocol version under which patient enrollment to begin. Updated based on FDA, CHMP/EMA and PMDA comments and advice to adjust inclusion/exclusion and study evaluations and to clarify and require study activity that address these comments.
3.0	03 Feb 2017	Protocol version to clarify and make slight modifications to inclusion/exclusion criteria. Updated to include Japan specific PMDA requirements to global protocol version and to add more clear parameters for patients to qualify and consent to continued study treatment after disease progression.
3.1	28 APR 2017	Protocol amendment to clarify contraception method and to accommodate request for earlier confirmation of disease progression for patients who continue study treatment beyond initial progression, according to FDA and MHRA comments.
3.1DEU	28 JUN 2017	Germany specific protocol amendment to clarify contraception method and to add additional pregnancy testing according to BfArM (Germany) comments.
3.1FRA	28 JUN 2017	France specific protocol amendment to modify inclusion and exclusion criteria, treatment suspension and discontinuation plan, and additional pregnancy tests according to ANSM request.
3.1UK	19 OCT 2017	UK specific amendment to clarify wording per UK REC comments.
3.1POL	16 NOV 2017	Poland specific protocol amendment to add additional pregnancy testing according to Poland competent authority comments.
4.0	07 FEB 2018	Change of inclusion criteria to allow for later line study treatment in some study regions where recent approval of therapy or standardization of therapy in later line has occurred. This is to maintain the target study population to be subjects who failed approved standard therapies.
4.0 Country Specific	22 MAR 2018	Country specific cascaded versions to reflect changes made in V4.0 from V3.1, including 4.0DEU, 4.0FRA, 4.0UK, and 4.0POL
4.0ROM	29 MAR 2018	Romania specific protocol amendment to add additional pregnancy testing according to Romania competent authority comments.
4.1 (Japan only)	04 JUN 2018	Extended trial period estimation as required by PMDA.
5.0	16 NOV 2018	Created open-label extension period for patients taking apatinib after unblinding study results during final analysis. Extended trial period estimation. Clarified ECG data collection. Integrated previous country specific protocol versions.
5.0FRA	16 NOV 2018	France specific version to reflect changes made in V5.0 from V4.0.

SYNOPSIS

Name of Sponsor	LSK BioPartners, Inc.
Protocol No.	LSK-AM301
Study Title	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)
Indication	Advanced or Metastatic Gastric Cancer
Investigational Product	YN968D1 (apatinib mesylate) will be supplied as 100 mg and 200 mg tablets for oral (PO) administration
Coordinating Investigator(s)	[redacted] [redacted] Korea For UK: [redacted] [redacted] UK
Study Centers	The study will be performed in approximately 90 sites in Asia Pacific, North America and Europe.
Study Duration	Total study duration will be approximately 30 months: 21 months of recruitment period + 9 months of treatment period, approximately from January 15th, 2017 to June30th, 2020. The extension period may continue beyond these dates. The study data will be analyzed 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 apatinib treatment, after final analysis and subsequent unblinding, will be given an option to consent to continue treatment with apatinib. Placebo patients will stop taking the placebo and will be monitored for survival status until death.
Study Phase	Phase III
Objective	<u>Primary objective</u> To evaluate the overall survival (OS) of Apatinib compared to Placebo in patients with Advanced or Metastatic Gastric Cancer (GC) <u>Secondary objectives</u> • 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, sVEGFR3 • To evaluate pharmacokinetics • To evaluate the safety: Adverse events, laboratory tests, vital signs, physical examination, 12-lead ECG, ECOG performance status
Study Design	Prospective, Randomized, Double-Blinded, Placebo-Controlled, Multinational, Multicenter, Parallel-group
Sample Size	Approximately 459 subjects (among them, the anticipated number of Japanese patients is at least 50 and up to 100 will be enrolled.)
Test Drug	Apatinib 700 mg p.o. qd (as 869 mg apatinib mesylate)
Control Drug	Matching Placebo to Apatinib
Treatments	Apatinib or Placebo, qd, p.o. should be continued until disease progression, intolerable toxicity or subject's withdrawal of consent.
Dose Adjustment Scheme	During each administration cycle (28 days/cycle), only a single dose reduction (Apatinib 700 mg qd to 600 mg qd or 600 mg qd to 400 mg qd) is permitted; A total of two dose reductions are permitted during the entire study period; and dose reduction below 400 mg qd will not be permitted. ・ In case of Grade I non-hematological treatment related toxicity and Grade I or II hematologic toxicity, no dose adjustment needs to be done. ・ In case of Grade II non-hematological treatment related toxicity, study treatment is continued without modification and with required symptomatic treatment. The investigator may reduce the dose by one level in the next cycle if they determine that continuing Grade II treatment related toxicity or a significant potential of worsening should be avoided. ・ In case of potentially related or related anti-angiogenic treatment Grade II AEs, pre-emptive dose reduction is recommended and the investigator may reduce the dose by one level at any time to reduce the risk of potential significant worsening that may cause the patient to discontinue the study. If the AE Grade stabilizes or decreases with dose reduction, the investigator may choose to

	increase the dose by one level at any time within the cycle or at the start of the next cycle to maximize potential study treatment exposure. The investigator may decrease or increase the dose according to tolerability of the patient of Grade II AEs, but may not decrease below the 400 mg qd dose level and may not increase above the 700 mg qd dose level. ・ In case of Grade III or IV non-hematological treatment related toxicity, study treatment will be temporarily withheld and resumed upon recovery to ≤ Grade I within 3 weeks. If treatment is resumed upon recovery, the dose should be reduced by one level. If recovery takes longer than 3 weeks, the investigator should contact the sponsor to determine if the patient may continue on study treatment. ・ In case of Grade III or IV hematological treatment related toxicity, study treatment will be temporarily withheld and resumed upon recovery to ≤ Grade II within 3 weeks. If treatment is resumed upon recovery, the dose should be reduced by one level. If recovery takes longer than 3 weeks, the investigator should contact the sponsor to determine if the patient may continue on study treatment.
Criteria for Discontinuation of Study Treatment	If any of the following criteria is met during the treatment period, the study treatment will be discontinued. The subject will undergo end-of-treatment examination (at completion/ discontinuation) and proceed to the post-treatment observation period to the full extent possible. 1. Subject withdraws his/her consent. 2. The development of disease progression is confirmed according to the RECIST guideline (version 1.1) that makes it inappropriate to continue with study treatment according to the investigator's discretion or consent for continued treatment beyond RECIST confirmed disease progression is not obtained. 3. Clinical symptoms determined to be due to disease progression that makes it inappropriate to continue with study treatment according to the investigator's discretion or consent for continued treatment beyond clinical symptoms that are determined to be due to disease progression is not obtained. 4. Onset of CTCAE grade ≥ 3 hypertension for which a causal relationship to the investigational product cannot be ruled out. (However, the judgment on whether or not to continue the treatment

	will be made by the investigator.) 5. Not having received a dose of the investigational product within the past consecutive 3 weeks for specific reasons, such as the onset of a treatment related adverse event. 6. Treatment with prohibited concomitant medication of sufficient dose and duration to confound the study results or to make continuation or restarting of treatment within 3 weeks unsafe for the patient. 7. Intolerable toxicity even after 2 dose reductions. 8. Confirmed positive pregnancy test. 9. The subject is lost to follow-up. 10. The subject is dead. 11. The investigator determines that continuation of study treatment is not appropriate.
Eligibility Criteria	**Inclusion Criteria:** 1. Male or female at least 18 years old or older. 2. Documented primary diagnosis of histologic- or cytologic-confirmed adenocarcinoma of the stomach or gastroesophageal junction. 3. Patients have locally advanced unresectable or metastatic disease that has progressed since last treatment. 4. One or more measurable or nonmeasurable evaluable lesions per RECIST 1.1. 5. Patients should have failed or were intolerant to at least two prior lines of standard chemotherapies with each containing one or more of the following agents: o Fluoropyrimidine (IV 5-FU, capecitabine, or S-1), o platinum (cisplatin or oxaliplatin), o taxanes (paclitaxel or docetaxel) or epirubicin, o irinotecan, o trastuzumab in case of HER2-positive, o ramucirumab o nivolumab o pembrolizumab Previous treatments with experimental agents (except experimental antiangiogenic agents) alone or as part of the prior therapy lines are allowed but not mandatory. A maximum number of three prior therapy lines are allowed, unless nivolumab or pembrolizumab was used in a prior line, for which case a maximum of four prior therapy lines are allowed.

	(For the patients whose disease recurred within 24 weeks from the last dose of adjuvant anticancer chemotherapy, that adjuvant anticancer chemotherapy is counted as 1 prior chemotherapy line.) 6. Disease progression within 6 months after the last treatment. 7. Patients who have adequate bone-marrow, renal and liver function including; a. Hematologic: Absolute neutrophil count ≥ 1,500/mm^3, Platelets ≥ 100,000/mm^3, Hemoglobin ≥ 9.0 g/dL (Blood transfusion to meet the inclusion criteria within 2 weeks is not allowed.). b. Renal: Creatinine clearance (according to Cockcroft-Gault Equation or by 24 hr urine collection) > 50 mL/min and serum creatinine < 1.0 x ULN. c. Hepatic: Serum bilirubin < 1.5 x ULN, AST and ALT ≤ 3.0 x ULN (≤ 5.0 x UNL, if with liver metastasis). d. Blood coagulation tests: PTT and INR ≤ 1.5 x ULN and ≤ 1.5 x ULN, respectively. e. The patient's urinary protein should be < 2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥ 2+, then a 24-hour urine or urine protein/creatinine ratio must be collected and must demonstrate < 2 g of protein in 24 hours to allow participation in the study. 8. Patients whose Eastern Cooperative Oncology Group (ECOG) performance status are evaluated to be ≤ 1. 9. Expected survival of ≥ 12 weeks, in the opinion of the investigator. 10. Ability to swallow the investigational product tablets. 11. Female patients of child-bearing potential must have a negative serum or urine pregnancy test at the Screening Visit. Females must be surgically sterile, postmenopausal for at least 1 year prior to Screening Visit (no other medical cause involved) or must be using a highly effective method of birth control according to applicable guidelines. Acceptable methods of birth control include: combined estrogen-progestogen or progestogen-only hormone contraceptives [oral, non-oral, or implants], intrauterine contraceptive device or Intrauterine Contraceptive System that are approved or certified in Japan or applicable country. Other intrauterine contraceptive device, contraception double barrier methods such as condom, sponge, cervical cap and diaphragm with spermicides, if locally determined to be highly effective outside of

Japan or applicable country, may be considered as acceptable.

12. Ability and willingness to comply with the study protocol for the duration of the study and with follow-up procedures.

Exclusion Criteria:

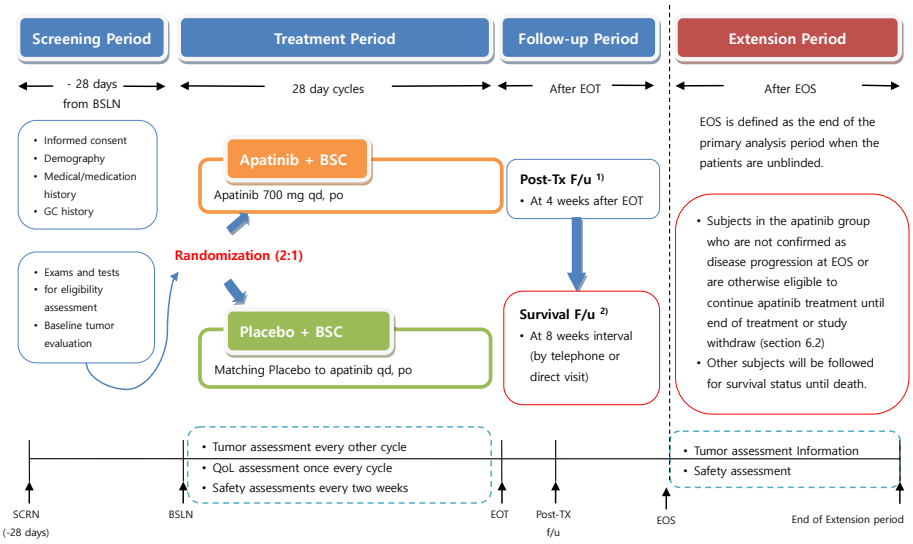
1. History of another malignancy within 2 years prior to randomization. Subjects with the following are eligible for this study if, in the opinion of the investigator, they do not pose a significant risk to life expectancy:
    - Bladder tumors considered superficial such as noninvasive (T1a) and carcinoma *in situ* (Tis)
    - Curatively treated cervical carcinoma *in situ*
    - Thyroid papillary cancer with prior treatment
    - Carcinoma of the skin without melanomatous features
    - Prostate cancer which has been surgically or medically treated and not likely to recur within 2 years
2. CNS metastases as shown by radiology records or clinical evidence of symptomatic CNS involvement in the last 3 months prior to randomization. Patients are eligible if metastases have been treated and have returned to neurologic baseline or are neurologically stable (except for residual signs or symptoms related to the CNS treatment).
3. Cytotoxic chemotherapy, surgery, immunotherapy, radiotherapy or other targeted therapies within 3weeks (4 weeks in cases of ramucirumab, mitomycin C, nitrosourea, lomustine; 1 week in case of biopsy) prior to randomization (Adjuvant radiotherapy given to local area for non-curative symptom relief is allowed until 2 weeks before randomization.).
4. Therapy with clinically significant systemic anticoagulant or antithrombotic agents within 7 days prior to randomization that may prevent blood clotting and, in the investigator's opinion, could place the subject at risk. Maximum dose of 325 mg/day of aspirin is allowed.
5. Patients who had therapeutic paracentesis of ascites (> 1L) within the 3 months prior to starting study treatment or who, in the opinion of the investigator, will likely need therapeutic paracentesis of ascites (> 1L) within 3 months of starting study treatment.
6. Previous treatment with Apatinib.

	7. Known hypersensitivity to Apatinib or components of the formulation. 8. Concomitant treatment with strong inhibitors or inducers of CYP3A4, CYP2C9 and CYP2C19. 9. Active bacterial infections. 10. Patients with substance abuse or medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results. Conditions include but are not limited to; - Known history of human immunodeficiency virus (HIV) infection. - Active hepatitis B or C infection or chronic hepatitis B or C infection requiring treatment with antiviral therapy or prophylactic antiviral therapy unless evidence of viral suppression has been documented and the patient will remain on appropriate antiviral therapy throughout the study. 11. Patients who participated, within 4 weeks prior to randomization, or are participating in any other clinical trial. 12. Pregnant or breast-feeding women. 13. History of drug or alcohol abuse within past 5 years. 14. Medical or psychiatric illnesses that, in the investigator's opinion, may impact the safety of the subject or the objectives of the study. 15. History of uncontrolled hypertension (Blood pressure $\geq$ 140/90 mmHg and change in antihypertensive medication within 7 days prior to randomization) that is not well managed by medication and the risk of which may be precipitated by a VEGF inhibitor therapy. 16. Patients who have known history of symptomatic congestive heart failure (New York Heart Association III-IV), symptomatic or poorly controlled cardiac arrhythmia, complete left bundle branch block, bifascicular block, or any clinically significant ST segment and/or T-wave abnormalities, QTcF > 450 msec for males or QTcF > 470 msec for females prior to randomization. 17. Prior major surgery or fracture within 3 weeks prior to randomization or presence of any non-healing wound (procedures such as catheter placement is not considered to be major). 18. History of bleeding diathesis or clinically significant bleeding within 14 days prior to randomization. 19. History of clinically significant thrombosis (bleeding or clotting disorder) within the past 3 months prior to randomization that, in the

	investigator's opinion, may place the patient at risk of side effects from anti-angiogenesis products. 20. History of gastrointestinal bleeding, gastric stress ulcerations, or peptic ulcer disease within the past 3 months prior to randomization that, in the investigator's opinion, may place the patient at risk of side effects from anti-angiogenesis products. 21. Myocardial infarction or unstable angina pectoris within 6 months prior to randomization. 22. History of severe adverse events including uncontrolled HTN or other common anti-angiogenesis class drug effects that were related to ramucirumab discontinuation and/or may indicate a higher risk to the safety of the patient if provided further anti-angiogenesis treatment, in the investigator's opinion. 23. History of other significant cardiovascular diseases or vascular diseases within the last 6 months prior to randomization (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 patient on VEGF inhibitor therapy. 24. History of clinically significant glomerulonephritis, biopsy-proven tubulointerstitial nephritis, crystal nephropathy, or other renal insufficiencies. 25. Gastrointestinal malabsorption, or any other condition that in the opinion of the investigator might affect the absorption of the study drug.
Study Overview	This is 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 who failed two or more prior treatment regimens. After informed consent and screening procedures, eligible subjects will be randomized in a 2:1 ratio to Apatinib 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. $\geq 4^{th}$). Randomized subjects will receive either the test product Apatinib 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 and 400 mg for Apatinib) are allowed during the entire study period according to the dose adjustment plan (refer to Section 4.4) Tumor response and progression will be assessed every other cycle (8 weeks interval) by a local imaging facility. Patient 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 analyzed post-study by a central imaging analysis facility. Centrally imaging results will determine the patient's 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 weeks interval till the death of the subject or closure of the study. **Extension Period:** Continued treatment with apatinib and best supportive care or best supportive care alone during the extension period of the study is only for those subjects that are taking either apatinib or placebo at the time of unblinding, respectively. For all other subjects that have not been considered as reaching the end of study (i.e. subjects in survival follow-up) and are not taking study medication at the time of unblinding, they will be followed for survival status only. It is anticipated that less than 40 subjects will be taking study medication at the time of unblinding of which less than 30 will be taking apatinib. Subjects taking apatinib at the time of unblinding: After the End of the Study (EOS) when the study is unblinded, subjects still on apatinib treatment with best supportive care, if determined to be safe to continue therapy by the investigator, may consent to continue this treatment until disease progression, intolerability, death, withdrawal of consent, or, if none of those has occurred, apatinib becomes available through other methods acceptable to the applicable regulatory authority. Site visit and evaluation for safety should be

	performed approximately every four weeks (± 3 days). Safety assessment may be performed more frequently, if clinically indicated. Tumor assessments will be performed per standard care approximately every 6-8 weeks. Subjects who reached end of treatment should be followed for survival per section 3.4.6. For apatinib subjects not willing to consent for further treatment after the study is unblinded or for those where the protocol extension period has not been approved locally or nationally, will stop the apatinib administration and perform the End of Treatment visit, Post-treatment Follow-up for safety, and Survival Follow-up as appropriate. A study schedule for subjects continuing apatinib treatment in the extension period is provided in Table 2. Subjects taking placebo at the time of unblinding: Subjects who are determined to be taking the placebo and best supportive care when the study is unblinded may consent to continue to be followed for survival status and continued best supportive care. For those subjects that were taking placebo, no End of Treatment visit is required. Best supportive care may be continued for patients no longer taking placebo, if appropriate, and only until other anti-cancer therapy is administered, disease progression, intolerability, death, or withdrawal of consent. The study schedule for subjects receiving only best supportive care in the extension period is to be determined by the investigator as standard of care for managing that supportive care. **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 Caucasians 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 Apatinib in 18 healthy volunteers of each of three specific ethnic populations; Japanese, Chinese and Caucasian. Initiation of enrollment in Japan will have a safety run-in approach to further confirm the safety of the study starting dose in this ethnic population. [Detail explanation is provided in Section 3.1.1]



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 till the death of the subject or until the study closure.

Endpoints

Primary Outcome Measure:

- Overall Survival (OS): Time from randomization to death. Subjects alive or lost to follow-up at the end of study (EOS) are censored.

Secondary Outcome Measures:

- Progression Free Survival (PFS): Time from randomization to either radiological progression or death. Subjects alive and free of progression at the end of study (EOS) are censored.
- Objective Response Rate (ORR): Percentage 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, partial response, or stable disease.
- Global health status/quality of life score according to European Organization 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.

Safety Measures:

- Adverse events, laboratory tests, vital signs, physical examination,

	12-lead ECG, and ECOG performance status. Exploratory Measures: ・ Pharmacodynamic marker: Vascular Endothelial Growth Factor (VEGF), sVEGFR-1, sVEGFR2 and sVEGFR3. ・ Pharmacokinetics
Statistical Methods	**Efficacy analysis** The primary analysis of OS will be conducted in the ITT population (all randomized subjects) using a stratified (by the randomization stratification factors) logrank test at the two-sided alpha=0.05 level of significance. If the primary analysis of OS is statistically significant, then the key secondary endpoints of PFS and ORR will be analyzed using a fixed-sequence testing procedure. First, PFS will be analyzed using the same statistical methods that are used in the primary efficacy analysis of OS. If the analysis of PFS is statistically significant, then ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. However, if a prior test is not statistically significant, then the subsequent analyses will be exploratory rather than confirmatory. All other secondary efficacy endpoints will be analyzed using two-sided tests at the alpha=0.05 level of significance, with no adjustments for multiplicity DCR will be analyzed using the same methodology as described for ORR. For the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire, the treatment groups will be compared using analysis of covariance (ANCOVA) models with treatment group and the randomization stratification variables as factors, and with the baseline value of the corresponding endpoint as a covariate. **Safety analysis** Safety parameter data will be summarized and listed by patient. Summary tables will show incidence rates (number of subjects with at least one event) of AE, SAE, etc., as well as summaries of severity (CTCAE v4.03) and causal relationship. Change from baseline tables will be presented for clinical laboratory assessments, vital signs and ECOG performance score. Laboratory abnormalities will also be

	summarized in tables showing shifts in grade.
Interim Analysis and IDMC	An interim analysis for futility will be conducted with collected clinical data when approximately 163 events (death) are observed. The independent data monitoring committee (IDMC) will review the result of the interim analysis and recommend to the sponsor whether or not to terminate for futility. Final decision regarding study termination will be made by the sponsor. Early termination will be considered if the calculated conditional power based on primary efficacy endpoint is less than 0.2.

Table 1. Study Schedule

Visit	SCRN		Treatment Period						EOT/DC	Post-Tx F/U	Survival F/U
			Cycle 1			All subsequent Cycles			-	EOT + 4 wks	Every 8 wks after Post-Tx F/U
Visit date	**≤ 28**	**≤ 14**	**1 (BSLN)**	**15**	**29***	**1***	**15**	**29**	**-**	**EOT + 28 days**	**-**
Visit window	**-**	**-**	**-**	**± 3 days**					**± 7 days**		
Informed consent	X										
Demography	X										
Medical history[1]	X										
GC history[2]	X										
Height & weight[3]		X	X¥	X		X¥	X		X	X	
Physical examination		X	X¥	X		X¥	X		X	X	
Vital signs[4]		X	X¥	X		X¥	X		X	X	
ECOG performance		X	X¥	X		X¥	X		X	X	
12-lead ECG		X	X¥[20]	X[20]		X¥[20]			X	X	
Chest X-ray			As clinically indicated								
Hematology[5]		X		X		X¥	X		X	X	
Blood chemistry[6]		X		X		X¥	X		X	X	
Coagulation tests[7]		X		X		X¥	X		X	X	
Urinalysis[8]		X		X		X¥	X		X	X	
Pregnancy test[9]		X	As clinically indicated or per local regulatory requirement[10]								
Serological test[11]		X									
QOL[12]			X¥			X¥			X		
CT (or PET-CT) or MRI		X						X[13]	X[13]		

Visit	SCRN		Treatment Period						EOT/DC	Post-Tx F/U	Survival F/U
			Cycle 1			All subsequent Cycles			-	EOT + 4 wks	Every 8 wks after Post-Tx F/U
Visit date	**≤ 28**	**≤ 14**	**1 (BSLN)**	**15**	**29***	**1***	**15**	**29**	**-**	**EOT + 28 days**	**-**
Visit window	**-**	**-**	**-**	**± 3 days**					**± 7 days**		
Biopsy[14]		As clinically indicated									
Eligibility review		X									
Randomization			X								
IP administration (qd)			X	X	X	X	X	X			
Adverse Events[15]	X	X	X	X	X	X	X	X	X	X	
Previous/Concomitant Medication[16]	X	X	X	X	X	X	X	X	X	X	
PD markers[17]			X¥			X¥			X		
PK sampling [18]			X	X		X					
Survival F/U[19]											X

1 cycle = 28 days, SCRN, Screening; BSLN, Baseline; W, Week; wks, weeks; EOT, End of Treatment; F/U, Follow-Up; Tx, Treatment; DC, Discontinuation; EOS, End of Study

*Note: Typically, Day 29 evaluations (adverse events and concomitant medication) of each cycle will not require a clinic visit and will not be performed if the patient is returning for Day 1 of the next cycle within the visit window (+ or – 3 days).

¥ Procedures should be performed before IP administration on the day of start.

1) Medical history within 1 year (within 3 years for cancer) from signing on the ICF should be collected. Medical history includes clinically significant past and current diagnosis including surgical procedures. Any surgical procedures done for treatment of GC will be collected separately regardless when those were carried out.
2) Full history of GC including date of initial diagnosis, primary location ([≥ 5 cm below GEJ] vs. GEJ), stage, metastatic and prior treatment information should be collected.
3) Height is measured once at Screening visit.

4) Vital signs include weight, sitting systolic/diastolic blood pressure, heart rate, respiration rate, and body temperature.
5) Hematology test (complete blood count, CBC) to be performed locally must include white blood cell (WBC) with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, absolute neutrophil count (ANC), red blood cell (RBC), hemoglobin (Hb), and hematocrit (Hct). If hematological treatment related toxicity occurs, the hematological test can be performed more frequently at the investigator's discretion during the treatment period.
6) Chemistry test to be performed locally must include sodium, potassium, chloride, carbon dioxide or bicarbonate (if required), blood urea nitrogen (BUN), creatinine, glucose (Fasting glucose at the Screening visit. Further fasting glucose only if necessary in the opinion of the investigator), total protein, albumin, calcium, amylase, lipase, phosphorous, magnesium, creatinine kinase (CK), uric acid, total bilirubin, AST, ALT, and ALP. If non-hematological treatment related toxicity occurs, the chemistry test can be performed at the investigator's discretion during the treatment period.
7) Coagulation test to be performed locally includes prothrombin time expressed as either prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT or aPTT).
8) Urinalysis test to be performed locally includes specific gravity, protein, glucose, occult blood, and, only if indicated, with microscopic examination.
9) This will be ordered only for women of child-bearing potential (serum or urine) including women who have not been surgically sterile, or post-menopausal for at least 1 year prior to Screening visit (no other medical cause involved).
10) Additional pregnancy test may be performed if required by local health authorities. Additional pregnancy test is required at the beginning every treatment cycle, and at EOT visit for Germany and Romania. Additional pregnancy test is required at the beginning of every treatment cycle, at EOT visit, and at post-treatment follow-up visit for Poland.
11) Serological tests to be performed locally include HIV antibody (if HIV antibody result is positive, HIV-1 antibody and HIV-2 antibody should be conducted), HBs antigen, and HCV antibody.
12) Subjects will complete two questionnaires; EORTC-QLQ-30 with EORTC QLQ-STO22 and EQ-5D-5L at baseline and then approximately every 4 weeks typically either at the end of the cycle or at the beginning of the next cycle.
13) Tumor will be assessed based on chest, abdominal and pelvic CT (or PET-CT) scan or MRI approximately every 8 weeks at the end of every other cycle. The same method should be used for the assessment of tumor response throughout the study. RECIST Guideline Version 1.1 will be used to assess tumor response. CT (or PET-CT) scan/MRIs after Baseline are allowed to perform within 7 days prior to the planned visit date. Scans to confirm progression of disease or for other reasons not per schedule as determined by the investigator may be performed when needed.
14) If a diagnosis cannot be made with chest, abdominal and pelvic CT (or PET-CT)/MRI due to atypical radiological appearance, primary or metastatic biopsy is recommended. Subsequent biopsies are carried out based on the investigator's discretion but it should be considered in case of growth or change in the enhancement pattern identified during follow-up. Histopathologic examination of the biopsy specimen should be assessed by an expert pathologist.

15) Adverse events will be documented for any untoward medical occurrence in a patient from the time they sign the informed consent form and until study completion per the Study Schedule.
16) Any medications administered within 28 days prior to signing the ICF and current medications should be collected. Medications for treatment of GC will be collected separately regardless when those were administered.
17) PD markers include vascular endothelial growth factor (VEGF), sVEGFR-1, sVEGFR2 and sVEGFR3.
18) PK sampling will be performed once prior to dosing on Day 1 of every cycle until EOT and at further timepoints on Day 1 of Cycle 1 and Day 15 of Cycle 1. Details are provided in Section 5.4.4 and in the PK Sampling Manual.
19) Subjects who prematurely discontinue study treatment but who are not withdrawn from the study will be followed every 8 weeks (± 7 days) for tracking of their survival until death or the end of the study. This survival follow-up should be performed via telephone, certified letter or during subjects' visit to the investigational site or other clinic site where confirmation of survival information documentation can be obtained. In addition, publicly accessible data may be used to document death. More frequent follow-up may be necessary at the time of the interim and final analysis to provide the most up-to-date survival information.
20) 12-lead ECG will be performed within 14 days before the date of randomization, at Day 1 of every cycle (before IP administration), at EOT visit and at the post-treatment follow-up visit. In addition to this, 12-lead ECG should be performed approximately 4 hours after IP administration on Cycle 1 Day 1 and Cycle 1 Day 15 corresponding to the same time when the PK C_{max} blood is drawn.

Table 2. Study Schedule for Subjects Continuing Apatinib Treatment into the Extension Period

Visit	Treatment Period during Extension All Cycles	EOT/DC	Post-Tx F/U EOT + 4 wks	Survival F/U Every 8 wks after Post-Tx F/U
Visit date	**1***	**-**	**EOT + 28 days**	**-**
Visit window	**± 3 days**	**± 7 days**		
Informed consent for extension period	X[1]			
IP dispensation	X			
Adverse Events	X	X	X	
Concomitant Medication	X	X	X	
CT (or PET-CT) or MRI[2]	X[2]	X[2]		
Targeted Physical examination	X¥		X	
Vital signs[3]	X¥		X	
12-lead ECG	X¥		X	
Hematology[4]	X¥		X	
Blood chemistry[5]	X¥		X	
Coagulation tests[6]	X¥		X	
Urinalysis[7]	X¥		X	
Survival F/U[8]				X
Chest X-ray	As clinically indicated			
Pregnancy test[9]	As clinically indicated or per local regulatory requirement[10]			

¥ Procedures should be performed before IP administration on the day of start.

1) Additional informed consent is required to enter extension study for placebo and apatinib subjects. After consent, placebo subjects will continue best supportive care and survival follow-up only.
2) Tumor will be assessed based on chest, abdominal and pelvic CT (or PET-CT) scan or MRI with a frequency as determined by standard of care

approximately every 8 weeks at the end of every other cycle. It is recommended, but not required, that the same tumor assessment criteria used during the study continue in the extension period. The same method should be used for the assessment of tumor response throughout the study. RECIST Guideline Version 1.1 will be used to assess tumor response. CT (or PET-CT) scan/MRIs after Baseline are allowed to be performed per standard of care. Scans to confirm progression of disease or for other reasons not per schedule as determined by the investigator may be performed when needed.

3) Vital signs include weight, sitting systolic/diastolic blood pressure, heart rate, respiration rate, and body temperature.
4) Hematology test (complete blood count, CBC) to be performed locally must include white blood cell (WBC) with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, absolute neutrophil count (ANC), red blood cell (RBC), hemoglobin (Hb), and hematocrit (Hct). If hematological treatment related toxicity occurs, the hematological test can be performed more frequently at the investigator's discretion during the treatment period.
5) Chemistry test to be performed locally must include sodium, potassium, chloride, carbon dioxide or bicarbonate (if required), blood urea nitrogen (BUN), creatinine, glucose (Fasting glucose at the Screening visit. Further fasting glucose only if necessary in the opinion of the investigator), total protein, albumin, calcium, amylase, lipase, phosphorous, magnesium, creatinine kinase (CK), uric acid, total bilirubin, AST, ALT, and ALP. If non-hematological treatment related toxicity occurs, the chemistry test can be performed at the investigator's discretion during the treatment period.
6) Coagulation test to be performed locally includes prothrombin time expressed as either prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT or aPTT).
7) Urinalysis test to be performed locally includes specific gravity, protein, glucose, occult blood, and, only if indicated, with microscopic examination.
8) Subjects who discontinue apatinib treatment during the extension period but who are not withdrawn from the study will be followed approximately every 8 weeks (± 7 days) for tracking of their survival until death or the end of the study. This survival follow-up should be performed via telephone, certified letter or during subjects' visit to the investigational site or other clinic site where confirmation of survival information documentation can be obtained. In addition, publicly accessible data may be used to document death. More frequent follow-up may be necessary at the time of the end of the study or for periodic updates to provide the most up-to-date survival information.
9) This will be ordered only for women of child-bearing potential (serum or urine) including women who have not been surgically sterile, or post-menopausal for at least 1 year prior to Screening visit (no other medical cause involved).
10) Additional pregnancy test may be performed if required by local health authorities. Additional pregnancy test is required at the beginning every treatment cycle, and at EOT visit for Germany and Romania. Additional pregnancy test is required at the beginning of every treatment cycle, at EOT visit, and at post-treatment follow-up visit for Poland.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-FU	5-Fluorouracil
ADL	Activity of Daily Living
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
AUC_{0-24}	Area under plasma concentration-time curve
BP	Blood Pressure
BSC	Best Supportive Care
BSLN	Baseline
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CF	Cisplatin; 5-fluorouracil
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatinine Kinase
C_{max}	maximum plasma concentration
CNS	Central Nervous System
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 Organization 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
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 Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
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 Tomography
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
TIA	Transient Ischemic Attack
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

1.1. Background

Gastric cancer is the 4th most common cancer world-wide and is the 4th most common cause of cancer-related death.[1] The prevalence rate of gastric cancer is higher in Asian, South America and Eastern Europe than in Western Europe and North America.[2]

Surgical resection is effective for complete cure of gastric cancer, but is only applicable to localized disease. A majority of patients have locally advanced, metastatic, or recurrent cancer that is inoperable. For such patients, extending the duration of survival by systemic chemotherapy is the primary treatment, and platinum and/or 5-FU based combination chemotherapy is widely used globally. As a first-line standard chemotherapy, multiple-agent combination chemotherapy is used, such as DCF (docetaxel; cisplatin; 5-fluorouracil) in the US, ECF (epirubicin; cisplatin; 5-fluorouracil) in Europe, CF (cisplatin; 5-fluorouracil either as infusional 5-FU or oral fluoropyrimidines like capecitabine or S-1) in Korea.[3]

According to several recent meta-analyses which analyzed the role of chemotherapy in patients with inoperable or metastasized gastric cancer, conservative chemotherapy is reported to improve survival and quality of life compared to the best supportive care.[4, 5, 6] However, the response rate for first-line therapy in advanced gastric patients is below 50%, and even in those fortunate cases that respond to the first-line chemotherapy, many patients re-experience tumor progression over time, often developing peritoneal metastasis and experiencing rapid exacerbation of systemic conditions. This results in 20~50% of patients requiring second-line chemotherapy in actual clinical practice.[7] A typical treatment therapy of advanced and metastatic gastric cancer is a combination therapy of capecitabine and oxaliplatin, which was not inferior in overall survival compared to 5-FU-based therapy with no significant difference in response rate. Such results indicate that capecitabine, an oral 5-FU analog, may replace the continuous intravenous infusion of 5-FU and supported that the combination therapy of capecitabine and oxaliplatin is a globally acceptable standard therapy.[8, 9]

As such, existing cytotoxic chemotherapies are based on fluoropyrimidine, cisplatin and anthracycline which can increase the oncological effect by combining two or three drugs rather than one, but improvement in 5-year survival is around 30–35%[10, 11, 12] and median overall survival only reaches 9~11 months for inoperable advanced gastric cancer.[8] In addition, combination therapy of chemotherapy agents may increase

anticancer effect but also increases the risk of toxicity. Many gastric cancer patients are elderly and also have other diseases which may limit the use of chemotherapy agents. Therefore, to improve disadvantages of the existing anticancer therapies such as treatment toxicity, inconvenient administration method, limited survival extension, development of new chemotherapies and drugs for targeted treatment is warranted.[13]

Drugs developed for targeted therapy of gastric cancer can be functionally broken into (1) HER2 signaling pathway inhibitors, (2) EGFR signaling pathway inhibitors and (3) Neovascular inhibitors, while the inhibitors for fibroblast growth factors (FGFs), mTOR and MET pathway have also been developed recently and are being studied for clinical application.[14]

Trastuzumab (Herceptin®) among the molecular targeted therapies of gastric cancer is anti-HER2 monoclonal antibody, a HER2 signaling pathway inhibitor, and a combination therapy of Trastuzumab and chemotherapy in gastric cancer patients with HER2 overexpression has been approved by the US FDA, Europe's EMEA and Korea in 2010. This was based on the result drawn from the ToGA (Trastuzumab for Gastric Cancer) study in gastric cancer patients with HER2 overexpression that adding Trastuzumab significantly improves the duration of survival (13.8 months vs. 11.1 months, p = 0.0046).[15]

Gefitinib and Erlotinib, Epidermal growth factor receptor (EGFR) signaling pathway inhibitors, did not show a significant effect on gastric cancer as a tyrosine kinase inhibitor of EGFR-1.[16, 17] In addition, cetuximab and panitumumab, anti-EGFR monoclonal antibodies, were assessed in phase III study. The median PFS for patients allocated capecitabine-cisplatin plus cetuximab was 4.4 months (95% CI 4.2-5.5) compared with 5.6 months (95% CI 5.1-5.7) for patients allocated capecitabine-cisplatin alone (HR 1.09, 95% CI 0.92-1.29; p-value=0.32) in cetuximab phase III study, EXPAND study.[18] For panitumumab phase III study, REAL-3 study, the median overall survival in patients allocated EOC (epirubicin, oxaliplatin, capecitabine) was 11.3 months (95% CI 9.6-13.0) compared with 8.8 months (95% CI 7.7-9.8) in patients allocated modified-dose EOC plus panitumumab (HR 1.37, 95% CI 1.07-1.76; p-value=0.013). These studies showed negative results.[19]

However, vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor, Ramucirumab is a fully human monoclonal antibody (IgG1) and has recently obtained approval in the US and is being used because the mean overall survival was at least 20% greater for the Ramucirumab (5.2 months) group than for the Placebo group (3.8 months)

in a phase III study (REGARD study). [20, 21, 22] In addition, the combination of ramucirumab with paclitaxel significantly increases overall survival compared with placebo plus paclitaxel (9.6 months vs. 7.4 months, HR 0.807 [95% CI 0.678-0.962; p-value=0.017]) in a phase III study (RAINBOW study). Based on the results, ramucirumab is recommended as a standard second-line treatment for patients with advanced gastric cancer.[23]

These drugs have less toxicity than existing anticancer drugs and have an advantage of allowing patient-tailored treatment as they are designed to react to signaling pathways specific to cancer. Lately in addition, clinical studies on new compounds of tyrosine kinases receptor inhibitors which suppress vascular angiogenesis, growth and metastasis are being carried out. Vascular endothelial cell growth factor (VEGF) is a circulating signal protein and because it induces a number of vascular angiogenesis-related responses such as cell proliferation or migration, vascular infiltration, and movement from bone marrow to stem cells when combined with a VEGF receptor (VEGFR), VEGF and VEGFR become physiologically important targets. An anti-VEGF monoclonal antibody, Bevacizumab, was evaluated in phase III study, and the AVAGAST study is the first antiangiogenic agents trial in gastric cancer. Even though the study did not show significant improvement of the OS (bevacizumab plus chemotherapy: 12.1 months vs. placebo plus chemotherapy: 10.1 months; HR 0.87 [95% CI 0.79 – 1.03; p-value=0.1002]), adding bevacizumab to chemotherapy was associated with significant increases in both PFS (6.7 months vs. 5.3 months; HR 0.80 [95% CI 0.68 – 0.93]) and ORR (46.0% vs. 37.4%; p-value=0.0315) in the first-line treatment of advanced gastric cancer.[24]

The VEGFR family is comprised of VEGFR1/Flt-1, VEGFR2/KDR/Flk-1 and VEGFR3/Flt-4. Various inhibitors which target the VEGFR family, including sorafenib, vandetanib, cediranib, and sunitinib, have been developed to date. These are all non-specific VEGF receptor small molecule inhibitors. Sorafenib achieved an approval for advanced renal cancer [25] and liver cancer [26]. Sunitinib achieved approval for gastrointestinal stromal tumor[27] and advanced renal cell cancer[28] and has been studied for advanced or metastatic gastric cancer.[29]

1.2. General Information

The family members of VEGF receptors include: VEGFR-1(Flt-1), VEGFR-2 (KDR/Flk-1), VEGFR-3 (Flt-4). Vascular angiogenesis in tumors is mainly induced by VEGF binding to VEGFR-2 (KDR/Flk-I). VEGFR-2 signaling in tumor vascular endothelial cells is now

recognized as a pivotal and rate-limiting step in tumor angiogenesis, and much research has focused on generating novel agents that inhibit this pathway. Most human tumors produce a high level of VEGF to trigger production of vasculature necessary to sustain tumor growth. Recently there have been several new drug candidates targeting inhibition of tyrosine kinase activity by inhibiting the VEGF receptors.

Apatinib is an orally administered small molecule receptor tyrosine kinase inhibitor (TKI) which selectively inhibits VEGFR-2 to suppress endothelial cell migration and proliferation and, by reducing the tumor microvascular density, induces an antiangiogenic effect and antineoplastic effect. Clinical study results of Apatinib are summarized in the following.

YN968D1 is the mesylate salt of apatinib freebase. Many prior studies were conducted referring to dose of apatinib as the weight of apatinib including the mesylate salt. In this study and in future studies, LSK will refer to apatinib dose strength as the weight of the apatinib freebase alone instead of weight of the apatinib mesylate salt. The freebase dosage is approximately 81% of the mesylate dosage. The formulation is the same. Referring to apatinib dose strength as freebase is more aligned with standards for referencing total active product.

1) Phase I, dose escalation, PK study in subjects with advanced cancer[30]

A phase I dose escalation study was conducted in China from August 2007 to March 2009, which enrolled 46 subjects at [redacted]. Of these, 19 subjects were enrolled in a dose-escalation study. Another 27 subjects were enrolled in the PK study. The subjects enrolled primarily were gastrointestinal tumor (73.9%). All subjects had received at least one prior chemotherapy regimen, 84.7% had prior surgery and 27% had radiation treatment. Measurable lesions were documented in 45 of the subjects at baseline. Subjects were treated for up to 56 days of continuous therapy and all subjects in the study received a total of 133 cycles of therapy.

The study was conducted at five dose levels (250 mg, 500 mg, 750 mg, 850 mg, and 1,000 mg of YN968D1 [as apatinib mesylate]). One (1) additional subject was included in the 250 mg-cohort due to withdrawal of consent of another participant. Two (2) DLTs at the dose level of 1,000 mg/day were documented. One (1) subject had Grade 3 hypertension and the other had Grade 3 hand-foot syndrome (HFS). Three additional subjects were enrolled in the 850 mg group. None of the total six (6) subjects in the 850 mg-cohort experienced DLTs. Therefore, the MTD for this dosing schedule was

determined to be 850 mg daily of YN968D1.

Pharmacokinetic assessments were also conducted on eleven (11) subjects in the 750 mg-single-dose cohort who continued to the 750 mg-multiple-dose cohort after a 7-day-washed-out period while one withdrew consent. Thus, the PK analysis population for single-dosing was n = 8 for 500 mg-cohort, n = 12 for 750 mg-cohort, n = 8 for 850 mg-cohort (one subject from the dose-escalation cohort provided consent to participate in the PK cohort), and for multiple-dosing 750 mg-cohort (n = 11) for 56 days.

The overall mean pharmacokinetic parameters of YN968D1 after single and multiple oral dose administration are summarized in Table 3 below. For single dose evaluation, C_{max} was achieved in 3 to 4 hours after oral administration. The plasma level of YN968D1 varied considerably between patients. The concentration of YN968D1 in plasma increased with dose. C_{max} and AUC_{0-24} showed a dose-dependent increase at doses from 500 to 850 mg, whereas increased slightly more than dose proportionally at dose of 850 mg dose, and showed high inter-individual variability. The elimination half-life of the terminal phase ($t_{1/2\lambda z}$), estimated to be approximately 9 hours, was consistent over the three dose levels.

For multiple-dose at 750 mg, the mean C_{max} was 2,421 ng/mL on Day 1, which increased to 2,553 ng/mL by Day 6, and the mean AUC_{0-24} was 19,399 ng·h/mL on Day 1, which increased to 25,449 ng·h/mL by Day 6. There was no further increase in C_{max} and AUC beyond 6 days of multiple dosing, and this was similar for the mean elimination $t_{1/2}$. Steady-state conditions were achieved by Day 6, suggesting no accumulation during 56 days of once-daily dosing.

Table 3. Noncompartmental Mean Pharmacokinetic Parameters of YN968D1 after Single or Multiple Oral Doses

PK Parameter	Single Oral Dose			Multiple Oral Dose of 750 mg			
	500 mg (n=8)	750 mg (n=12)	850 mg (n=8)	Day 1 (n=11)	Day 6 (n=11)	Day 28 (n=11)	Day 56 (n=11)
C_{max} ng/mL (%CV)	1,521 (75.1)	2,379 (55.9)	2,833 (90.0)	2,421 (68.5)	2,553 (52.8)	2,210 (45.5)	1,854 (51.2)
t_{max} hour (range)	3.5 (3.0-8.0)	3.0 (2.0-4.0)	4.0 (1.5-8.0)	3.0 (2.0-8.0)	4.0 (3.0-8.0)	4.0 (2.0-6.0)	3.0 (2.0-6.0)

PK Parameter	Single Oral Dose			Multiple Oral Dose of 750 mg			
	500 mg (n=8)	750 mg (n=12)	850 mg (n=8)	Day 1 (n=11)	Day 6 (n=11)	Day 28 (n=11)	Day 56 (n=11)
AUC_{0-24} ng.hr/mL (%CV)	11,295 (68.7)	18.172 (59.3)	21,975 (80.8)	19,399 (60.5)	25,449 (59.2)	19,946 (43.2)	15,629 (63.2)
$t_{1/2\lambda z}$ hours (%CV)	8.1 (30.7)	9.0 (15.1)	9.1 (33.1)	8.9 (25.8)	11.0 (56.7)	11.3 (66.5)	8.3 (61.0)

Abbreviations: C_{max}, maximum plasma concentration; CV, coefficient of variation; t_{max}, time to reach C_{max}; AUC_{0-24}, area under plasma concentration-time curve; $t_{1/2\lambda z}$, half-life associate with terminal slope of a semilogarithmic concentration-time curve

The safety population comprised all subjects who had received at least 1 dose of YN968D1 (N=46). The most frequently observed adverse drug reactions were hypertension (69.5%, 29 grade 1-2 and 3 grade 3-4), proteinuria (47.8%, 16 grade 1-2 and 6 grade 3-4), and hand-foot syndrome (45.6%, 15 grade 1-2 and 6 grade 3-4). Hypertension was generally manageable with antihypertensive agents. Approximately 10 % of the subjects who developed HFS progressed to Grade 3. Other treatment-related AEs were generally mild or moderate in severity and were manageable. The treatment was discontinued for both of the two subjects who experienced DLT. After recovery, one (1) subject was able to reinitiate treatment at a reduced dose. A total of 15 subjects received at least one cycle of YN968D1 at the initial dose. Four (4) subjects discontinued the treatment during Cycle 1, of which 1 subject in the 250 mg dose group due to disease progression and 3 in the 1,000 mg dose group due to intolerable toxicity. Eighteen (18) subjects had a dose reduction for different toxicities during the extended treatment (1 in 1,000 mg group, 13 in 850 mg group, and 4 in 750 mg group). For those subjects who experienced dose reduction, the mean duration of treatment with YN968D1 was 5.4 months.

Among the 45 subjects with measurable lesions, 4 withdrew consent due to receiving other therapy, 1 experienced intolerable toxicity, and 3 were lost to follow-up. Therefore, 37 subjects were evaluable for best overall response. Partial response (PR) was observed in 7 (18.9%) subjects, stable disease (SD) in 24 subjects (64.9%), resulting in a disease control rate of 83.8% at 8 weeks. Subject's response at each dose level is provided in Table 4. Out of 7 subjects who achieved a partial response (PR), 1 was

diagnosed as gastrointestinal stromal tumor (GIST), 1 as cancer of unknown primary site, 1 as renal cell cancer, 1 as gastric cancer and 3 as colon cancer.

Table 4. Objective Response Observed in phase I YN968D1 Trial

Dose Cohort	Response in Evaluable Subjects				Disease Control (%)
	CR	PR	SD	PD	CR+PR+SD
250 mg	0	1	1	1	2 (66.7)
500 mg	0	2	4	3	6 (66.7)
750 mg	0	2	9	0	11 (100)
850 mg	0	2	8	1	10 (90.9)
1,000 mg	0	0	2	1	2 (66.7)
Total	0	7	24	6	31 (83.8)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

The results of this study showed that YN968D1 was safe and well tolerated and exhibited substantial antitumor activity at the YN968D1 (apatinib mesylate) dose of 750 mg and 850 mg once daily.

2) Phase II clinical study in patients with advanced or metastatic gastric cancer[31]

In the phase II study conducted in patients with advanced or metastatic gastric cancer who did not respond to the second-line anticancer therapy or had disease recurred, a total of 144 patients were randomized to 3 groups; placebo group (Group A), 850mg of YN968D1 (as apatinib mesylate) qd group (Group B) and 425mg of YN968D1 bid group (Group C).

Median overall survival (OS) of Group A, B and C was 2.50 months (95 % CI, 1.87-3.70 months), 4.83 months (95 % CI, 4.03-5.97 months) and 4.27 months (95 % CI, 3.83-4.77 months), respectively, and median progression-free survival (PFS) was 1.40 months (95 % CI, 1.20-1.83 months), 3.67 months (95 % CI, 2.17-6.80 months) and 3.20 months (95 % CI, 2.37-4.53 months), respectively. Both the PFS (P <0.001) and OS (P <0.001, P = 0.0017) showed a statistically significant difference between the YN968D1 group and the Placebo group. Nine patients had a PR (Group B n=3, Group C n=6). Toxicities were tolerable. Toxicities of Grade 3 or over were hand-foot syndrome and hypertension, and hematologic toxicities of Grade 3 or over were rare. Considering the safety profile of YN968D1 at the two dose levels of 850 mg and 425 mg, the dosing regimen of 850 mg

once daily of YN968D1 was recommended. To sum up, YN968D1 increased PFS and OS in patients with advanced gastric cancer who failed to second-line or higher anticancer therapy.

3) Phase III clinical study in patients with advanced or metastatic gastric cancer[32]

A multicenter, randomized, double-blind, phase III study was conducted in patients who failed to second-line therapy. The study was designed as 28 days/cycle, consisting of YN968D1 850 mg (as apatinib mesylate) group and Placebo group. The primary efficacy endpoint was overall survival. Randomization was done centrally and was stratified by the number of metastatic sites (≤2 or >2). A total of 267 randomly assigned subjects were included in FAS population; 176 in the YN968D1 group and 91 in the Placebo group. As for the efficacy, mean overall survival was statistically greater for the YN968D1 group than for the Placebo group (6.5 months versus 4.7 months; HR= 0.709; 95% CI (0.537~0.937); p< 0.0149). mPFS also showed the same result (2.6 months versus 1.8 months; HR= 0.444, 95%CI (0.331~0.595), P<0.001). ORR was 2.84% and 0.00% for the YN968D1 group and the Placebo group, respectively. As for the safety, YN968D1 was mostly controlled by treatment discontinuation or reduction. The most common adverse events were hand-foot skin reaction (HFSR), proteinuria and hypertension. In conclusion, the efficacy and safety of YN968D1 850 mg were confirmed in advanced and metastatic gastric cancer.

1.3. Study Rationale

In this phase III study, we will assess the benefit of YN968D1 treatment in advanced and metastatic gastric cancer patients who failed standard of treatment at 700 mg/day of YN968D1 (as apatinib mesylate), which was within the maximum tolerated dose in the phase I study[30], in terms of overall survival (OS), progression free survival (PFS), tumor response rate, disease control rate and quality of life. The target population will be advanced and metastatic gastric cancer patients who have failed approved standard treatments (disease progression or intolerant to available approved drugs).

YN968D1 is known to selectively inhibit VEGFR-2 and angiogenesis of cancer. Various laboratory tests showed results that YN968D1 highly selectively inhibits protein tyrosine kinase VEGFR-2/KDR (IC_{50} about 1 nM) receptor, and YN968D1 demonstrated an anticancer effect in gastric cancer cell line (NCI-N87 cell line) implanted-nude mouse. In mouse with hypodermic implantation of colorectal, liver, kidney, breast or non-small cell cancer cells, YN968D1 also demonstrated an anticancer effect. Also, a combination

therapy of oxaliplatin and YN968D1 showed a high cancer cell growth inhibitory effect while having no increase in toxicity.

As a result of phase I clinical study conducted in patients with advanced solid tumor[30], Apatinib mesylate had the MTD of 850 mg and the clinically recommended dose of 750 mg. The most common side effects were hypertension, proteinuria, and hand-foot syndrome but were all mild to moderate in severity and were manageable. In terms of effectiveness, a total 83.8% of patients had disease controlled; partial response in 18.9% and stable disease in 64.9%. Out of 22 patients with gastric-colorectal cancer who were included in the study, 18 showed a disease control effect where 4 of them were partial responses indicating an outstanding effect. Phase II and phase III clinical studies conducted in China showed a great effect of increasing overall survival compared to the Placebo group in patients with advanced gastric cancer[31, 32]. Based on the positive outcome, Apatinib has been approved in China for treatment of advanced gastric cancer in 2014.

Previous studies show clinical benefits in OS and PFS, however, there is no more treatment option for patients who failed approved standards therapies. As described above, Apatinib has shown potential survival benefit in patients with gastric cancer; therefore, its efficacy and safety need to be ascertained in this controlled and properly powered phase III study. This study will be the steppingstone to continue the clinical development of Apatinib 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.

2. STUDY OBJECTIVE

The overall objective of this study is 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).

2.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of Apatinib 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 Objectives

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 Apatinib 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 Apatinib plus Best Supportive Care (BSC) compared to Placebo plus BSC in patients with advanced or metastatic gastric cancer who failed two or more prior treatment regimens.

After informed consent and screening procedures, eligible subjects will be randomized in a 2:1 ratio to Apatinib 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. $\geq 4^{th}$).

Randomized subjects will receive either the test product Apatinib (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 Apatinib) are allowed during the entire study period according to the dose adjustment plan (refer to Section 4.4).

The intent of the study is to have subjects receive a dose every day continuously. The actual dose received will be captured and the start and stop of dosing will be used to calculate dose intensity and duration of treatment. A cycle length is determined by either the calendar days or days on treatment, whichever is appropriate for the individual subject. Dose interruptions such as for management of adverse events may elongate the cycle days as needed, however, the subject should be evaluated at reasonable intervals to ensure the subjects safety such as follow-up for adverse events and laboratory value monitoring. While continuously receiving study investigational product, per the protocol schedule, subjects should be evaluated at regular site visits, which will be made approximately every 2 weeks as described above.

Tumor response and progression will be assessed every other cycle (8 weeks interval) by a local imaging facility. Patient 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 analyzed post-study by a central imaging analysis facility. Centrally imaging results will determine the patient's 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. More frequent intervals of survival follow-up may be performed to provide for the most accurate survival data at the time of interim and final analysis or during periodic updates.

In this trial, approximately 459 subjects will be enrolled (among them, the anticipated number of Japanese patients is at least 50 and up to 100 will be enrolled.)

The study data will be analyzed 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 continuing to benefit from apatinib treatment, after final analysis and

subsequent unblinding, will be allowed to consent for extension of treatment with apatinib, if determined safe to continue treatment by the investigator, and best supportive care until proven intolerable, disease progression, death, the drug is commercially available or other reason for subject treatment withdrawal. Subjects who have been receiving placebo will be allowed to consent for extension of best supportive care only until the extension period is completed or the study is stopped by the sponsor. All subjects who are taking investigational product at the time of unblinding will be asked to consent for continued survival follow-up during the extension phase of the study. Subjects who were off treatment at the time of unblinding, but are still participating in the study (i.e. in survival follow-up) do not require a new consent after unblinding to continue participation.

3.1.1. Additional Information for 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 Apatinib in 18 healthy volunteers of each of three specific ethnic populations; Japanese, Chinese and Caucasian. Initiation of enrollment in Japan will have a safety run-in approach to further confirm the safety of the study starting dose in this ethnic population. Initially, in Japan, only 6 patients will be enrolled and assigned either Apatinib or Placebo to investigate the safety at the same starting dose and with the same randomization/enrollment criteria as all other study patients. The treatment assignment, as with all patients, will not be known to any study personnel with the following exceptions. During the observation period, the independent data monitoring committee or an appropriately unblinded and separate study personnel who would perform no other study activity or duties that would jeopardize the integrity of the study, will determine whether at least 3 of the 6 patients have been assigned to Apatinib treatment. The patients will be 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 is 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 have been assigned Apatinib treatment, the Apatinib treated patients will be observed for a minimum of 14 days of therapy. If less than 3 patients are randomized to Apatinib treatment, 3 more patients (bringing the total to 9 patients) may be enrolled immediately to ensure that the DLT evaluation in Japan patients is performed on at least 3 Apatinib treated patients.

If no DLT occurs during the DLT evaluation period (at least 0/3 Apatinib treated patients), the study may proceed in Japan with further enrollment per protocol and the IDMC and PMDA will be notified.

If there is only 1 DLT during the DLT evaluation period (at least 1/3), another 3 patients may be enrolled to ensure that at least 6 Apatinib patients are observed for the 14 day DLT evaluation period.

If there remains only 1 DLT during the DLT evaluation period after at least 6 Apatinib treated patients are observed (at most 1/6 Apatinib treated patients), the study may proceed in Japan with further enrollment per protocol and the IDMC and PMDA will be notified.

If there are 2 DLT events in the 14 day DLT evaluation period (either at most 2/3 or at least 2/6 Apatinib treated patients), the enrollment in Japan will temporarily stop until a decision to discontinue or continue enrollment with or without modifications is decided after consultation with the IDMC and PMDA.

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 Apatinib 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 or 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

3.2. Study Population

3.2.1. Inclusion Criteria

If a patient is to be eligible to participate in the study, the patient must meet all of the following inclusion criteria.

1. Male or female at least 18 years old or older.
2. Documented primary diagnosis of histologic- or cytologic-confirmed adenocarcinoma of the stomach or gastroesophageal junction.
3. Patients have locally advanced unresectable or metastatic disease that has progressed since last treatment.
4. One or more measurable or nonmeasurable evaluable lesions per RECIST 1.1.
5. Patients should have failed or were intolerant to at least two prior lines of standard chemotherapies with each containing one or more of the following agents:
    - fluoropyrimidine (IV 5-FU capecitabine, or S-1),
    - platinum (cisplatin or oxaliplatin),
    - taxanes (paclitaxel or docetaxel) or epirubicin,
    - irinotecan,
    - trastuzumab in case of HER2-positive
    - ramucirumab
    - nivolumab
    - pembrolizumab

    Previous treatments with experimental agents (except experimental antiangiogenic agents) alone or as part of the prior therapy lines are allowed but not mandatory. A maximum number of three prior therapy lines are allowed, unless nivolumab or pembrolizumab was used in a prior line, for which case a maximum of four prior therapy lines are allowed.

    (For the patients whose disease recurred within 24 weeks from the last dose of adjuvant anticancer chemotherapy, that adjuvant anticancer chemotherapy is counted as 1 prior chemotherapy line.)
6. Disease progression within 6 months after the last treatment.
7. Patients who have adequate bone-marrow, renal and liver function including;
    a. Hematologic: Absolute neutrophil count ≥ 1,500/mm^3, Platelets ≥ 100,000/mm^3, Hemoglobin ≥ 9.0 g/dL (Blood transfusion to meet the inclusion criteria within 2 weeks is not allowed.).
    b. Renal: Creatinine clearance (according to Cockcroft-Gault Equation or by 24 hr urine collection) > 50 mL/min and serum creatinine < 1.0 x ULN.

c. Hepatic: Serum bilirubin < 1.5 x ULN, AST and ALT ≤ 3.0 x ULN (≦ 5.0 x UNL, if with liver metastasis).
d. Blood coagulation tests: PTT and INR ≤ 1.5 x ULN and ≤ 1.5 x ULN, respectively.
e. The patient's urinary protein should be < 2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥ 2+, then a 24-hour urine or urine protein/creatinine ratio must be collected and must demonstrate < 2 g of protein in 24 hours to allow participation in the study.

8. Patients whose Eastern Cooperative Oncology Group (ECOG) performance status are evaluated to be ≤ 1.
9. Expected survival of ≥ 12 weeks, in the opinion of the investigator.
10. Ability to swallow the investigational product tablets.
11. Female patients of child-bearing potential must have a negative serum or urine pregnancy test at the Screening Visit. Females must be surgically sterile, postmenopausal for at least 1 year prior to Screening Visit (no other medical cause involved) or must be using a highly effective method of birth control according to applicable guidelines. Acceptable methods of birth control include: combined estrogen-progestogen or progestogen-only hormone contraceptives [oral, non-oral, or implants], intrauterine contraceptive device or Intrauterine Contraceptive System that are approved or certified in Japan or applicable country. Other intrauterine contraceptive device, contraception double barrier methods such as condom, sponge, cervical cap and diaphragm with spermicides, if locally determined to be highly effective outside of Japan or applicable country, may be considered as acceptable. Abstinence is not an acceptable method of contraception for the study.
12. Ability and willingness to comply with the study protocol for the duration of the study and with follow-up procedures.

3.2.2. Exclusion Criteria

If a patient is to be eligible to participate in the study, the patient must not meet any of the following exclusion criteria.

1. History of another malignancy within 2 years prior to randomization. Subjects with the following are eligible for this study if, in the opinion of the investigator, they do not pose a significant risk to life expectancy:
    - Bladder tumors considered superficial such as noninvasive (T1a) and carcinoma *in situ* (Tis)

- Curatively treated cervical carcinoma *in situ*
- Thyroid papillary cancer with prior treatment
- Carcinoma of the skin without melanomatous features
- Prostate cancer which has been surgically or medically treated and not likely to recur within 2 years

2. CNS metastases as shown by radiology records or clinical evidence of symptomatic CNS involvement in the last 3 months prior to randomization. Patients are eligible if metastases have been treated and have returned to neurologic baseline or are neurologically stable (except for residual signs or symptoms related to the CNS treatment).
3. Cytotoxic chemotherapy, surgery, immunotherapy, radiotherapy or other targeted therapies within 3 weeks (4 weeks in cases of ramucirumab, mitomycin C, nitrosourea, lomustine; 1 week in case of biopsy) prior to randomization (Adjuvant radiotherapy given to local area for non-curative symptom relief is allowed until 2 weeks before randomization.).
4. Therapy with clinically significant systemic anticoagulant or antithrombotic agents within 7 days prior to randomization that may prevent blood clotting and, in the investigator's opinion, could place the subject at risk. Maximum dose of 325 mg/day of aspirin is allowed.
5. Patients who had therapeutic paracentesis of ascites (> 1L) within the 3 months prior to starting study treatment or who, in the opinion of the investigator, will likely need therapeutic paracentesis of ascites (> 1L) within 3 months of starting study treatment.
6. Previous treatment with Apatinib.
7. Known hypersensitivity to Apatinib or components of the formulation.
8. Concomitant treatment with strong inhibitors or inducers of CYP3A4, CYP2C9 and CYP2C19.
9. Active bacterial infections.
10. Patients with substance abuse or medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results. Conditions include but are not limited to;
    - Known history of human immunodeficiency virus (HIV) infection.
    - Active hepatitis B or C infection or chronic hepatitis B or C infection requiring treatment with antiviral therapy or prophylactic antiviral therapy unless evidence of viral suppression has been documented and the patient will remain on appropriate antiviral therapy throughout the study.

11. Patients who participated, within 4 weeks prior to randomization, or are participating in any other clinical trial.
12. Pregnant or breast-feeding women.
13. History of drug or alcohol abuse within past 5 years.
14. Medical or psychiatric illnesses that, in the investigator's opinion, may impact the safety of the subject or the objectives of the study.
15. History of uncontrolled hypertension (Blood pressure ≥ 140/90 mmHg and change in antihypertensive medication within 7 days prior to randomization) that is not well managed by medication and the risk of which may be precipitated by a VEGF inhibitor therapy.
16. Patients who have known history of symptomatic congestive heart failure (New York Heart Association III-IV), symptomatic or poorly controlled cardiac arrhythmia, complete left bundle branch block, bifascicular block, or any clinically significant ST segment and/or T-wave abnormalities, QTcF > 450 msec for males or QTcF > 470 msec for females prior to randomization.
17. Prior major surgery or fracture within 3 weeks prior to randomization or presence of any non-healing wound (procedures such as catheter placement is not considered to be major).
18. History of bleeding diathesis or clinically significant bleeding within 14 days prior to randomization.
19. History of clinically significant thrombosis (bleeding or clotting disorder) within the past 3 months prior to randomization that, in the investigator's opinion, may place the patient at risk of side effects from anti-angiogenesis products.
20. History of gastrointestinal bleeding, gastric stress ulcerations, or peptic ulcer disease within the past 3 months prior to randomization that, in the investigator's opinion, may place the patient at risk of side effects from anti-angiogenesis products.
21. Myocardial infarction or unstable angina pectoris within 6 months prior to randomization.
22. History of severe adverse events including uncontrolled HTN or other common anti-angiogenesis class drug effects that were related to ramucirumab discontinuation and/or may indicate a higher risk to the safety of the patient if provided further anti-angiogenesis treatment, in the investigator's opinion.
23. History of other significant cardiovascular diseases or vascular diseases within the last 6 months prior to randomization (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 patient on VEGF inhibitor therapy.

24. History of clinically significant glomerulonephritis, biopsy-proven tubulointerstitial nephritis, crystal nephropathy, or other renal insufficiencies.
25. Gastrointestinal malabsorption, or any other condition that in the opinion of the investigator might affect the absorption of the study drug.

3.3. Discussion of Study Design

This study is a prospective, randomized, double-blinded, placebo-controlled, multinational, multicenter, parallel-group, phase III study to evaluate the efficacy and safety of Apatinib in patients with advanced or metastatic gastric cancer.

In the Chinese phase I study[30], Apatinib mesylate demonstrated noteworthy efficacy with 18 of 22 patients with gastro-colorectal cancer showing disease control. Of those 18 patients with disease control, 4 subjects showed partial response. The mean treatment duration in this phase I study was 5.4 months. In the phase I study[30], treatment with apatinib was given until disease progression, death, an intolerable toxicity or withdrawal of consent and the most frequent adverse events were hypertension, proteinuria and hand-foot syndrome, which were mild to moderate in severity and manageable. The phase I efficacy data showed that partial response was seen in 18.9% of patients and stable disease in 64.9%, totaling an 83.8% disease control rate. In other words, out of 22 patients with gastric-colorectal cancer in total who were included in this phase I study, 18 subjects had disease control including 4 subjects with partial response, which indicates an excellent efficacy profile. In the phase II and III studies recently conducted in China as mentioned above, Apatinib demonstrated an excellent efficacy that it increased overall survival compared to the Placebo group when administered to patients with advanced gastric cancer who failed two or more lines of therapy. Based on the results from the clinical studies, this phase III study is planned to confirm the effects of Apatinib in patients with advanced or metastatic gastric cancer. The subjects will be randomized at 2:1 ratio to receive either Apatinib (freebase) 700 mg qd or Placebo qd and then the safety and efficacy will be assessed during the treatment period.

In addition, this study has been designed as a double-blind, placebo-controlled, and multinational, multicenter study. The target population—advanced or metastatic gastric cancer patients who have failed standard therapies—is an appropriate candidate who will possibly benefit from Apatinib treatment considering there is no recommended or accessible further treatment. To reserve objectivity and credibility of the study results, a

double-blind design has been adopted. Patients will be stratified according to the geographic region (Asia vs. North America/Europe). Region was employed as a stratification factor in order to avoid an imbalance among regions in the randomization to the Apatinib group and the Placebo group. In addition, disease measurability (measurable vs. nonmeasurable), Prior ramucirumab treatment (Yes vs. No), and Treatment therapy line (3^{rd} vs. $\geq 4^{th}$) will be employed as stratification factors. The primary endpoint is overall survival (OS), which is considered the most reliable cancer endpoint and is the preferred endpoint from a regulatory perspective. Thus, OS was selected as the primary endpoint in this phase III trial. EORTC and EQ-5D questionnaires were selected in order to assess the quality of life of subjects because these questionnaires are being used in cancer patients worldwide.

3.4. Study Procedures

Protocol-specific evaluations and their schedule in detail during the whole study period are summarized in Table 1. in the protocol synopsis section. Figure 1 shows the overview of the study scheme.

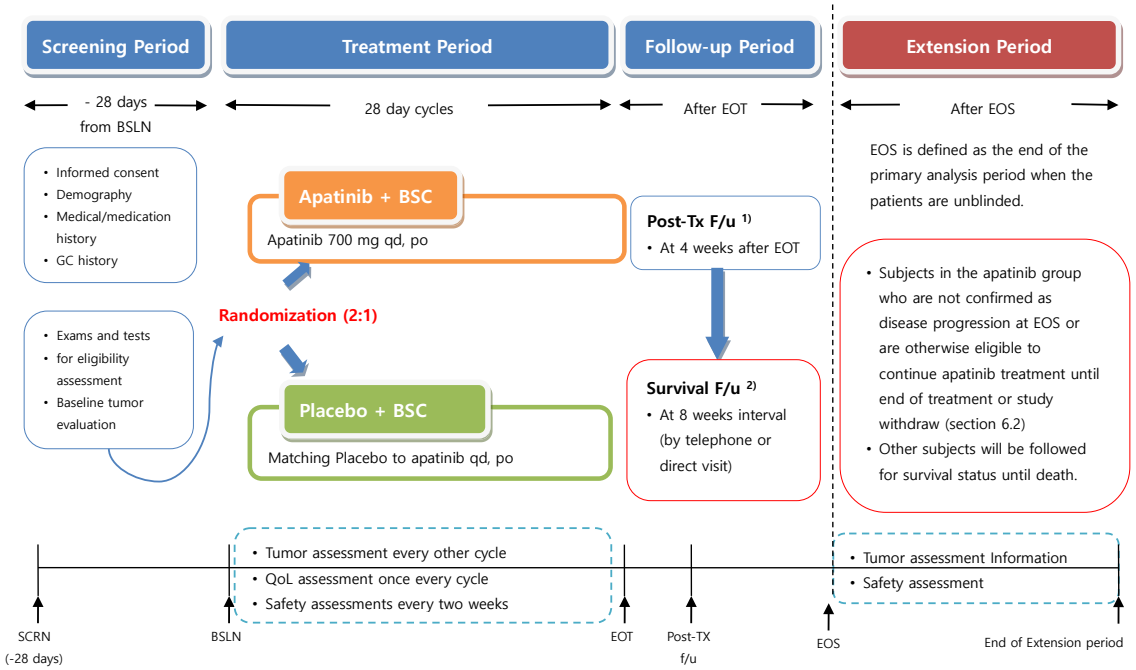


Figure 1. Study Scheme

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.

3.4.1. Screening Visit

Upon signing on the informed consent form, the screening period will start. Screening should be completed within 28 days before the date of randomization. Within this period, following procedures are to be carried out. Any procedures or assessments associated with the study should be initiated only after obtaining the written informed consent from potential subjects. If procedures within the 28-day window were performed as part of standard of care prior to consent, those evaluations may be used as screening period results.

- Informed consent[1]
- Collection of demographic information
- Collection of medical history[2]
- Collection of GC history[3]
- Collection of previous/concomitant medication information[4]
- Assessment of adverse events[5]

[1)] In Japan, when the patient is under 20 years old, informed consent will be obtained from both the patient and the legal guardian.
[2)] Medical history within 1 year (within 3 years for cancers) from signing on the ICF should be collected. Medical history includes clinically significant past and current diagnosis including surgical procedures. Any surgical procedures done for treatment of GC will be collected separately regardless when those were carried out.
[3)] Full history of GC including date of initial diagnosis, primary location ([≥ 5 cm below GEJ] vs. GEJ), stage, and metastatic information should be collected.
[4)] Any medications administered within 28 days from signing the ICF and current medications should be collected. Medications for treatment of GC will be collected separately regardless of when those were administered.
[5)] Any untoward medical occurrence in a patient who has signed the informed consent form will be collected as an adverse event.

The following should be completed within 14 days before the baseline visit. These data except vital signs, which will be measured again in the baseline visit, will be used as baseline data for determination of eligibility of subjects in the study.

- Measurement of height
- Physical examination
- Measurement of vital signs including weight

- Assessment of ECOG performance score
- 12-lead ECG
- Hematology, blood chemistry, serological test, coagulation test and urinalysis[1]
- Pregnancy test[2]
- CT/MRI for GC evaluation[3]
- Biopsy for GC evaluation[4]
- Collection of concomitant medication information
- Assessment of adverse event
- Eligibility review by the registration center[5)]

[1)] Please refer to 5.3.2 for specific item of each test panel.
[2)] This will be ordered only for women of child-bearing potential (serum or urine) including women who have not been post-menopausal for at least 1 year prior to Screening visit.
[3)] Tumor will be assessed based on CT (or PET-CT) scan or MRI. The same method should be used for the assessment of tumor response throughout the study.
[4)] If a diagnosis cannot be made with CT (or PET-CT)/MRI due to atypical radiological appearance, primary or metastatic tumor biopsy is recommended. Histopathologic examination of the biopsy specimen should be assessed by an expert pathologist.
[5)] Among the screened patients, the registration center will review those fulfilling the criteria in Section 3.2.1, not meeting any of the criteria in Section 3.2.2 and judged to be appropriate for the study.

3.4.2. Baseline Visit (Day 1 in Cycle 1)

Randomized subjects will receive the assigned investigational product as instructed. The following procedures are carried out at this visit.

- Physical examination
- Measurement of vital signs including weight
- Assessment of ECOG performance score
- 12-lead ECG (Before IP administration)
- Chest X-ray, pregnancy test (serum or urine), biopsy[1]
- Collection of concomitant medication information
- Randomization
- Completion of patient reported outcome (EORTC QLQ-C30, EORTC QLQ-STO22, EQ-5D-5L)

- Pharmacodynamic (PD) marker test
- Dispense of investigational product
- Administration of investigational product
- Blood sampling for Cycle 1 Day 1 PK
- 12-lead ECG (Approximately 4 hours after IP administration and corresponding to PK sampling)
- Assessment of adverse events

[1)] Only done when clinically indicated. The following countries require a pregnancy test at the beginning of each treatment cycle for the applicable subjects: Germany, Romania, and Poland.

If a randomized subject is found not to meet any of the eligibility criteria before the first administration of the investigational product, the subject will not be started on the study treatment and will be withdrawn from the study. Subjects who are randomized but never receive the investigational product or subjects who are withdrawn from the study before randomization will not be allowed to re-consent.

3.4.3. Treatment Visits After Baseline

A treatment cycle is composed of 28 days (4 weeks) and the study treatment will be continued until the death of the subject or discontinuation of the study treatment due to disease progression, intolerable toxicity or subject's withdrawal of consent. Subjects are required to visit the investigational site every 2 weeks (± 3 days) till the death of the subject or discontinuation of the study treatment due to disease progression, intolerable toxicity or subject's withdrawal of consent. The following procedures are carried out at each treatment visit after baseline.

- Physical examination
- Measurement of vital signs including weight
- Assessment of ECOG performance score
- Assessment of adverse event
- Collection of concomitant medication information
- Chest X-ray, pregnancy test (serum or urine), biopsy[1]
- 12-lead ECG and Pharmacodynamic (PD) marker test[2]
- Blood sampling for PK (See Section 5.4.4)
- Hematology, blood chemistry, coagulation test and urinalysis
- Completion of patient reported outcome (EORTC QLQ-C30, EORTC QLQ-STO22, and EQ-5D-5L)[2]

- CT/MRI[3]
- Dispense of investigational product at the first day of every cycle (as long as the study treatment is continued)

[1)] Only done when clinically indicated. Biopsies are carried out based on the investigator's discretion, but it should be considered in case of growth or change in the enhancement pattern identified during follow-up. Histopathologic examination of the biopsy specimen should be assessed by an expert pathologist. The following countries require a pregnancy test at the beginning of each treatment cycle for the applicable subjects: Germany, Romania, and Poland.
[2)] Measured at the first day of every cycle (4 weeks interval) prior to dosing. In addition, a 12-lead ECG should be performed approximately 4 hours after IP administration on Day 15 of Cycle 1 corresponding to the C_{max} PK blood draw timepoint.
[3)] Measured approximately every 8 weeks at the end of every other cycle from Baseline

3.4.4. End of Treatment (EOT) Visit/Discontinuation

Subjects who discontinue study treatment (see Section 6.2) or subjects permanently withdrawn from the study are required to make this visit within 7 days from their final administration of the investigational product. Following procedures are carried out at this visit.

- Physical examination
- Measurement of vital signs including weight
- Assessment of ECOG performance score
- Assessment of adverse event
- Collection of concomitant medication information
- Chest X-ray, pregnancy test (serum or urine), biopsy[1]
- 12-lead ECG
- Hematology, blood chemistry, coagulation test and urinalysis
- Pharmacodynamic (PD) marker test
- CT/MRI[2]
- Completion of patient reported outcome (EORTC QLQ-C30, EORTC QLQ-STO22, EQ-5D-5L)

[1)] Only done when clinically indicated. Biopsies are carried out based on the investigator's discretion but it should be considered in case of growth or change in

the enhancement pattern identified during follow-up. Histopathologic examination of the biopsy specimen should be assessed by an expert pathologist. The following countries require a pregnancy test at the end of treatment visit for applicable subjects: Germany, Romania, and Poland.

[2)] If CT/MRI is performed within 4 weeks prior to EOT or disease progression is clearly confirmed by previous CT/MRI, tumor evaluation is not required at EOT.

3.4.5. Post-Treatment Follow-Up Visit

For the purpose of safety follow-up, a post-treatment visit should be made at 28 days (± 7 days) after the end of treatment visit. The following procedures are carried out at this visit.

- Physical examination
- Measurement of vital signs including weight
- Assessment of ECOG performance score
- 12-lead ECG
- Hematology, blood chemistry, coagulation test and urinalysis
- Assessment of adverse event
- Collection of concomitant medication information
- Chest X-ray, pregnancy test (serum or urine)[1]

[1)] Only done when clinically indicated. A pregnancy test for applicable subjects is required at post-treatment follow up visit for Poland.

3.4.6. Survival Follow-Up Visit

Subjects who prematurely discontinue study treatment (see Section 6.2) but who are not withdrawn from the study will be followed-up at 8 weeks (± 7 days) interval for tracking of their survival until they meet the following criteria:

- The subject withdraws his/her consent on the study.
- The subject is dead.
- The entire study has been completed or discontinued.
- The investigator judges that it is necessary to discontinue the follow-up.

This survival follow up can be performed via telephone, certified letter or during subjects' visit to the investigational site or other clinic site where confirmation of survival information documentation can be obtained. In addition, publicly accessible data may be used to document death. The survival status and follow up date should be recorded in

the electronic case report form (eCRF).

The following parameters shall be recorded in the follow-up period (Post-Treatment Follow-Up Visit and Survival Follow Visit):

- The onset time of death or disease progression (if disease progression is not confirmed at EOT)
- Other tumor treatments (if applicable)

3.4.7. Extension period study visits

After the study is unblinded and the extension period of the study begins, all subjects taking study medication at that time should have their study treatment assignment unblinded and determined to be either apatinib or placebo. For subjects that are not taking study medication at the time of unblinding, the investigator may request to know their treatment assignment. Subjects who have stopped taking study medication or best supportive care prior to unblinding will not be given the option to restart taking apatinib or begin receiving best supportive care.

Subjects taking placebo at the time of unblinding:

Subjects who are determined to be taking the placebo and best supportive care when the study is unblinded may consent to continue to be followed for survival status and to continue best supportive care. For those subjects that were taking placebo, no End of Treatment visit is required. Best supportive care may be continued for patients no longer taking placebo, if appropriate, and only until other anti-cancer therapy is administered, disease progression, intolerability, death, or withdrawal of consent. No AE's or SAE's will be gathered for subjects receiving only best supportive care. Survival status will continue to be requested until withdrawal of consent. The study schedule for subjects receiving only best supportive care in the extension period is to be determined by the investigator as standard of care for managing that supportive care.

Subjects taking apatinib at the time of unblinding:

After the End of the Study (EOS) when the study is unblinded, for those subjects taking apatinib, if the investigator determines that it is safe to continue apatinib treatment, they should obtain consent from the subject to continue to administer apatinib and perform safety evaluations, tumor assessments and survival follow-up. Subjects will continue apatinib treatment until disease progression, intolerability, death, withdrawal of consent, or, if none of those has occurred, apatinib becomes available through other methods

acceptable to the applicable regulatory authority. Site visit and evaluation for safety should be performed approximately every four weeks (± 3 days). Safety assessment may be performed more frequently, if clinically indicated. Tumor assessments will be performed per standard care approximately every 6-8 weeks. Subjects who reached end of treatment should be followed for survival per section 3.4.6. For apatinib subjects not willing to consent for further treatment after the study is unblinded or for those where the protocol extension period has not been approved locally or nationally, will stop the apatinib administration and perform the End of Treatment visit, Post-treatment Follow-up for safety, and Survival Follow-up as appropriate.

Treatment Visits during Extension Period:

The following procedures are carried out at each treatment visit after the start of the extension period for each subject continuing apatinib treatment:

- Assessment of adverse event
- Dispense investigational product[1]
- Tumor assessment by CT/MRI[2]
- Targeted Physical examination, if needed
- Measurement of vital signs including weight
- 12-lead ECG
- Laboratory testing: Hematology, blood chemistry, coagulation test and urinalysis

[1)] Dispensed a 30-day supply when needed for as long as the study treatment is continued

[2)] Measured at standard of care intervals

If clinically indicated or regulatory required and as part of standard of care:

- Chest X-ray
- Pregnancy test (serum or urine)[1]

[1)] Additional pregnancy test is required at the beginning of every treatment cycle, and at EOT visit for Germany and Romania. Additional pregnancy test is required at the beginning of every treatment cycle, at EOT visit, and at post-treatment follow up visit for Poland.

Best Supportive Care during Extension Period (former placebo subjects):

Only subjects that were actively taking placebo at the time of unblinding will be given the option to continue with best supportive care treatment after discontinuation of the placebo. No procedures are required for subjects receiving only best supportive care during the extension period. The site and investigator should provide best supportive care as they were providing while the subject was on blinded placebo study medication. Best supportive care and any further evaluations of these subjects should be per standard of care and are not required to be reported. Best supportive care may be provided until beginning another anti-cancer therapy, disease progression or subject's withdrawal of consent. Survival follow-up should continue until the extension study is completed, the subject has expired or the subject withdraws consent.

4. STUDY TREATMENTS

4.1. Investigational Products

4.1.1. Identity and Storage of Investigational Products

All investigational products will be supplied by LSK BioPartners, Inc. in a polyvinylidene chloride (PVDC), heat-sealed foil-laminated blister pack. The outer packaging and the relevant unit of each pack of the investigational products will be labelled according to the applicable law to indicate these drugs are to be used only for investigational purposes. Apatinib is supplied as 200 mg and 100 mg tablets and the matching placebo will be also provided with the tablets of the same size.

Table 5. Identity of the Test Drug

Common Name	Apatinib
Chemical Name	N-(4-(1-cyanocyclopentyl) phenyl)-2-(4-pyridinylmethyl) amino-3-pyridinecarboxamide methanesulfonate
Molecular Formula	$C_{25}H_{27}N_5O_4S$
Molecular Weight	493.58

Matching placebos will be manufactured to appear the same as the equivalent strength Apatinib tablet with the same ingredients (only excipients are included).

The investigational products 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 its sponsor representative. Once a deviation is identified, the investigational product must be stored separately and not used until the sponsor or its sponsor representative provides written permission to use the investigational product.

4.1.2. Return of Unused Investigational Products

Subjects are required to bring all used packs and any unused investigational product (IP) when they visit to the site at the end of each cycle. The IP returned by subjects or any unused IP (that is, never dispensed to any subject) must be returned to the sponsor or its representative at the end of the study or destroyed after accountability has been performed and only after written authorization from the sponsor or sponsors representative has been received.

4.1.3. Discontinuation of Investigational Products Supply

During the Treatment period, all subjects will be provided with investigational products (Apatinib or Placebo) until treatment discontinuation.

If one of the following criteria is met, sponsor can discontinue IP supply.

1) The country applicable regulatory agency declines New Drug Application (NDA) for the indication.
2) This trial is terminated due to safety issue.
3) Apatinib becomes commercially available to the patients in the applicable country.
4) Other alternative standard treatment can be available.
5) The trial is unblinded and the extension period of the study is not approved by applicable regulatory or local ethics authorities.

4.2. Method of Assigning Patients to Treatment Group (Randomization method)

Subjects will be randomized in a 2:1 ratio to the Apatinib 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. nonmeasurable)
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.

4.3. 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.

4.4. Dose Adjustment Plan

To ensure safety of subjects, the dose of study treatment may be reduced for the toxicities described below as related to treatment, including ‘Certain, Probable or Possible’ causality.

- In case of Grade I non-hematological treatment related toxicity and Grade I or II hematologic toxicity, no dose adjustment needs to be done.
- In case of Grade II non-hematological treatment related toxicity, study treatment is continued without modification and with required symptomatic treatment. The investigator may reduce the dose by one level in the next cycle if they determine that continuing Grade II treatment related toxicity or a significant potential of worsening should be avoided.
- In case of potentially related or related anti-angiogenic treatment Grade II AEs, pre-emptive dose reduction is recommended and the investigator may reduce the dose by one level at any time to reduce the risk of potential significant worsening that may cause the patient to discontinue the study. If the AE Grade stabilizes or decreases with dose reduction, the investigator may choose to increase the dose by one level at any time within the cycle or at the start of the next cycle to maximize potential study treatment exposure. The investigator may decrease or increase the dose

according to tolerability of the patient of Grade II AEs, but may not decrease below the 400 mg qd dose level and may not increase above the 700 mg qd dose level.

- In case of Grade III or IV non-hematological treatment related toxicity, study treatment will be temporarily withheld and resumed upon recovery to ≤ Grade I within 3 weeks. If treatment is resumed upon recovery, the dose should be reduced by one level. If recovery takes longer than 3 weeks, the investigator should contact the sponsor to determine if the patient may continue on study treatment.
- In case of Grade III or IV hematological treatment related toxicity, study treatment will be temporarily withheld and resumed upon recovery to ≤ Grade II within 3 weeks. If treatment is resumed upon recovery, the dose should be reduced by one level. If recovery takes longer than 3 weeks, the investigator should contact the sponsor to determine if the patient may continue on study treatment.

During each administration cycle (28 days/cycle), only a single dose reduction (700 mg qd to 600 mg qd or 600 mg qd to 400 mg qd) is permitted; A total of two dose reductions are permitted during the entire study period; and dose reduction below 400 mg qd will not be permitted.

4.5. Double-Blinding Method

4.5.1. Double-Blinding

All investigational products that were made indistinguishable between study drug and matching placebo in appearance for the purpose of double-blinding will be supplied to the investigators and will be identified by code numbers.

4.5.2. Maintenance of Blinding

Allocation to either the Apatinib group or the Placebo group will be double-blinded. As Apatinib-matching placebo will be supplied, the Apatinib group and the Placebo group cannot be distinguished at the time of the delivery and dispensing of the investigational product. Double-blindness of the study is maintained by prohibiting subjects and investigators as well as any study personnel of the sponsor or CRO except for the persons in charge of randomization codes and labelling of IP from accessing randomization codes.

The allocation code of a given subject can be broken according to the unblinding procedures described in Section 4.5.3 only if medically necessary to treat intercurrent illness or medical emergency, or according to the sponsor's judgment that the code must be broken to protect the rights and safety of the subject.

4.5.3. Unblinding Procedure in Emergency Situations

Unblinding should only occur when medically necessary to treat an intercurrent illness or medical emergency. When the treatment information assigned to a subject need to be revealed emergently in order to appropriately treat an intercurrent illness or medical emergency, the investigator will request an emergency code break for the subject by entering the necessary data into IWRS according to a written procedure prepared separately. A discussion with the medical monitor for the sponsor (or sponsor's designee) should occur when possible to review alternatives to unblinding that could be taken. If there can be no discussion with the medical monitor for the sponsor (or sponsor's designee) before unblinding the emergency code, this should be documented.

In response to the request for an emergency code break, the emergency code for the subject will immediately be unblinded via IWRS. IWRS will notify the investigator of the treatment information assigned to the subject, and will also notify the sponsor and its representative of the unblinding.

4.6. Treatment Compliance

The investigator and/or the designated person responsible for dispensing investigational products (IP) must be able to account for all IP provided to the site. The person responsible for dispensing the IP must document the dispensing detail (the subject number, the date, the amount of dispensed IP, the lot number of IP, the IP code on each IP package dispensed, etc.) and have access to the Interactive Web Response System (IWRS). Dose modification, interruptions, and reason for these actions must be recorded in the source documents. No IP is to be used other than for the purpose of this study.

4.7. Prior and Concomitant Medications

4.7.1. Contraindicated Treatment

The following treatments or medications are contraindicated during the Treatment period. If any of these treatments/medications is administered, the subject should be withdrawn from the study treatment.

- While patients are on treatment cycle of this study, 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 products from other

clinical studies are not permitted.

- The use of hematopoietic factors such as G-CSF etc. during the Japan DLT assessment period will be prohibited in the protocol.
- Packed red blood cell transfusion or erythropoietin therapy are not permitted within 14 days prior to the study enrollment (however, permitted if stable condition was maintained by erythropoietin therapy for at least 1 month prior to the enrollment). Packed red blood cell transfusion or erythropoietin therapy can be used after the initiation of the treatment at the investigator's discretion and their use must be recorded in the eCRF. (Erythropoietin therapy is not approved for the anemia associated with cancer chemotherapy in Japan)
- Medications known or suspected to prolong the QT/QTc interval, with the exception of drugs with low risk of QT/QTc prolongation. This includes but 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
- Strong inducers or inhibitors of CYP3A4, CYP2C9, and CYP2C19. This includes but not limited to the following drugs (refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm);
  - CYP3A4 inducers or inhibitors: Diltiazem, Itraconazole, Ketoconazole, Posaconazole, Voriconazole, Clarithromycin
  - CYP2C9:Phenytoin, Piroxicam
  - CYP2C19: Rifampin, Fluconazole, Fluoxetine, Fluvoxamine
- During the treatment period, the intake of following food and supplements are prohibited in principle. If the patients are not under the control of hospital, the patients will be informed that following foods are to be avoided;
  - Supplements St. John's wort (Hypericum perforatum)

- Foods and drinks that contains grapefruit, seville orange or orange marmalade

4.7.2. Permitted Concomitant Treatment

Any medications that are considered necessary for the subject's welfare may be given at the discretion of the investigator and are permitted. Medications for treatment of underlying disease and symptomatic treatment of adverse events are permitted.

Best supportive care (BSC) will be given to subjects in the both treatment groups at the discretion of the investigators. BSC is defined as palliative, non-cancer therapy. There should be no difference in the practice of administering BSC between the two groups and BSC will be continuously provided after the study treatment is discontinued.

5. ASSESSMENT MEASURES

5.1. Baseline Assessment

5.1.1. Demographics

At the time of screening, demographic information including age, sex, body mass index, race will be collected from those who were identified as potential subjects.

5.1.2. Medical and Surgical History

At the Screening Visit, the subject's treatment history of gastric cancer as well as his/her medical and surgical history will be recorded. All medical history within 1 year prior to screening (within 3 years for cancers) from signing on the ICF will be collected. History of gastric cancer shall include date of diagnosis, diagnosis result, location of primary tumor at diagnosis (Gastric [$\geq$ 5 cm below GEJ] vs. GEJ), information of metastasis (metastases to other organs such as lung, liver metastasis), surgical history etc.

5.1.3. Prior Medications History

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. Any changes or additions in concomitant medications or therapies shall be indicated in the eCRF.

Any prior anticancer treatments used for the management of advanced or metastatic gastric cancer (e.g. anticancer chemotherapy and/or radiotherapy) and number of lines shall be identified and recorded in the eCRF.

5.2. Efficacy Assessment

5.2.1. Tumor Evaluation (Chest, abdominal and pelvic CT/MRI)

Tumor imaging will be further explained in an Imaging manual. A CT should be used with slice thickness ≤ 5 mm. Tumor will be assessed CT (or PET-CT) scan or MRI—whichever is used, the same method and the same equipment should be used throughout the study—at the following time points:

- Within 14 days before Baseline visit (baseline measurement)
- The end of every other cycle thereafter
- End of treatment (EOT) visit[1)]

[1)] If CT/MRI is performed within 4 weeks prior to EOT or disease progression is clearly confirmed by previous CT/MRI, tumor evaluation is not required at EOT.
If a subject is withdrawn from the IP treatment due to any reason except for disease progression, tumor evaluation will be continued every 8 weeks until disease progression is confirmed or other tumor treatment is initiated.

The change of imaging equipment will be allowed only if subjects 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 key images to be used for determination of disease progression will be reviewed by a central imaging analysis facility based on objective tumor assessments using the RECIST guidelines (version 1.1). The tumor response criteria is presented in Appendix 2.

If a diagnosis cannot be made with CT/MRI due to atypical radiological appearance, primary or metastatic biopsy is recommended. Subsequent biopsies are carried out based on the investigator’s discretion, but it should be considered in case of growth or change in the enhancement pattern identified during follow-up. Histopathologic examination of the biopsy specimen should be assessed by an expert pathologist.

5.2.2. Patient Reported Outcome

Following two questionnaires will be used as tools to collect patient reported outcomes. These questionnaires will be completed at the first day of every cycle (4 weeks interval).

- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-the gastric cancer

specific module (EORTC QLQ-STO22): EORTC QLQ-C30 is a 30-item core-cancer-specific questionnaire-integrating system for assessing the health-related QOL of cancer patients 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 patients (e.g., constipation, diarrhea, 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.[33, 34] The questionnaire is widely used in cancer patients including gastric cancer[23, 35,36] and has been translated in various languages. It should be completed by subjects. In addition, EORTC QLQ-STO22 is a 22-item gastric cancer-specific questionnaire-integrating system for assessing the health-related QOL of gastric cancer patients.

- EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire: it has been developed by EuroQol Group from the EQ-5D-3L, which has 3 levels in each dimension, to improve the instrument's sensitivity and to reduce ceiling effects. 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. Its validity and reliability have been proven in many different populations, including subjects with gastric cancer.[37, 38] It should be completed by subjects.

5.3. Safety Assessment

5.3.1. Adverse Event

Assessments will be made on the adverse events (AEs) including any sign, symptom, disease or illness that occurred newly or if present at baseline, worsened in a subject and may impair the well-being of the subject. Clinical laboratory findings and any other findings from the diagnostic procedures that are considered clinically significant (e.g. requiring unscheduled diagnostic procedures or treatment modalities or resulting in discontinuation of the study) will also be included in the AE assessment.

AEs will be collected and evaluated at each visit after informed consent is signed until 28 calendar days after the last administration of the investigational product. Any AEs that emerged following administration of IP will be evaluated in comparison to the baseline level of AEs determined at screening.

See Section 7 for detailed information on SAFETY REPORT of this study.

5.3.2. Clinical Laboratory Tests

The following tests will be performed locally at individual investigational sites. Hematology, chemistry, coagulation and urinalysis will be performed at Day 1 (before IP administration) and Day 15 of every cycle, the end of treatment (EOT) visit and the post-tx F/U visit. If hematological or non-hematological treatment related toxicity occurs, laboratory tests can be performed at the investigator's discretion during the treatment period. Serological tests will be performed only at the screening visit and additional tests can be performed as clinically indicated or as required by local health authorities.

- 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).

5.3.3. Vital Signs and Physical Findings

Body temperature (oral, axillary, core, temporal, or tympanic), blood pressure (systolic/diastolic), heart rate, and respiratory rate will be collected as vital signs. Vital signs will be measured at every visit with the subject in a sitting position at rest for at least 5 minutes. Systemic physical examination will be performed within 14 days before the date of randomization and at every study visit thereafter.

5.3.4. Weight and Height

Weight (kg) will be measured at each visit and height (cm) will be measured only at the screening visit.

5.3.5. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (refer to Appendix 1) will be assessed at every visit.

5.3.6. ECG Monitoring

A 12-lead ECG should be performed within 14 days before the date of randomization, at Day 1 of every cycle (before IP administration), at EOT visit and at the post-treatment follow-up visit. In addition, a 12-lead ECG should be performed approximately 4 hours after IP administration on Cycle 1 Day 1 and Cycle 1 Day 15. Additional ECG should be performed as clinically indicated. Any abnormal findings in ECG measurements with clinical significance should be reported as adverse events.

To facilitate the safety analysis in section 8.3.7 of the ECG data, if approved by country and local regulatory authorities, duplicate copies (either digital or hard copies) of the ECG tracing and the evaluation report should be transferred to the Sponsor after de-identifying the subject information for further clinical evaluation of ECG data as per regulatory recommendations. The original ECG results will be kept on file at the site as source documentation. Handling of this information/data will be done in accordance with the applicable data protection laws. (US government CFR 21 Part 11 for electronic records; US government Health Insurance Portability and Accountability Act (HIPPA), etc.)

As the request for the ECG copies is during an amendment, it is typically necessary to either ensure that informed consent is obtained to facilitate submittal of these ECG copies to the sponsor (or sponsor representatives) or in the case where consent cannot be updated (i.e. subject has expired), appropriate local ethics committee approval is obtained to authorize the submittal of these ECG copies.

5.3.7. Chest X-Ray

A chest x-ray should be performed as clinically indicated. Any abnormal findings in chest x-ray measurements with clinical significance should be reported as adverse events.

5.4. Exploratory Assessment

5.4.1. Pharmacodynamic (PD) marker

At baseline, all subjects will be tested for Single-Nucleotide Polymorphisms (SNPs) to identify genotypes associated with the response to therapy with VEGFR-2 inhibitor.

Vascular Endothelial Growth Factor (VEGF) will be evaluated at;

- The 1st day of 1st cycle
- The 1st day of 2nd cycle and each cycle thereafter (prior to IP administration)
- End of Treatment visit

In addition, plasma samples for sVEGFR-1, sVEGFR2 and sVEGFR3 will be taken.

Guidelines for collection and handling of blood specimen and materials will be provided by the sponsor or sponsor's designee. Each study site collects and ships the specimens to the central laboratory according to the guidelines provided.

Genetic test will be conducted including the gene information that specifies the patient and will be used only for research purpose. Therefore, the results of genetic test will not be disclosed to the patient, patient's family, investigators, or other third parties and will not be recorded in the patient's medical record.

In Japan, if the patient is under 20 years old and the patient or legal guardian withdraws consent, the collection and sampling of blood sample will be stopped. However, the information and blood samples already collected and sampled can be used to evaluate the result of the clinical trial.

5.4.2. Biological Sample Storage

The sponsor may wish to analyze blood samples in the future for the research purpose. Blood samples will be tested and 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. Samples should be frozen at site and will be shipped to the sponsor or its designee during or at the end of the study as requested by the sponsor.

5.4.3. Tumor Biopsy

The sponsor may wish to analyze tumor biopsy samples in the future for the research purpose. Tumor biopsy (primary or metastatic tumor) will be collected whenever possible during the treatment period.

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. Tumor tissue samples should be fixed by formalin at site and will be shipped to the sponsor or its designee during or at the end of the study as requested by the sponsor.

Testing of biologic and/or tumor tissue samples may include but is not limited to the following tests;

- Growth factors; EGFR, VEGFR, HER2, c-MET
- Cytokines
- Cell cycle regulators, apoptosis-associated factors
- miRNAs; Let-7g, miR-433, miR-214, miR-21
- Epigenetic alterations, Genetic polymorphisms

5.4.4. Pharmacokinetics

Pharmacokinetic parameters (C_{max}, T_{max}, AUC, half-life, etc.) will be evaluated for apatinib. Blood samples for determination of plasma PK profiles of apatinib will be collected during the study per the time table below. The allowed time window for sampling is ± 10 minutes.

Time Point	Sample Number	Time (h)
Cycle 1/Day 1	1 2	Predose 3–4 h postdose (T_{max})
Cycle 1/Day 15	3 4 5 6 (from 20±5% of patients)	Predose on Day 15 0.5–1 h postdose 3–4 h postdose (T_{max}) 8–12 h postdose
Cycle 2/Day 1 – Cycle 9/Day 1*	7–14*	Predose only (trough)

* or until drug discontinuation or study completion

For PK sample for each pharmacokinetic evaluation, a total of 5~10 mL of blood will be collected at each time point. Collection, handling and storage of blood samples for determination of plasma PK profiles of apatinib will be explained in the study instructional manual.

6. CRITERIA FOR STUDY DISCONTINUATION OR SUBJECT WITHDRAWAL

6.1. Early Termination of the Study

The study may be terminated at any time by the sponsor for any reason. Some reasons may be due to new safety information, non-compliance issues, or judgment of study futility. In this event, the sponsor will inform the study Investigators, investigational sites, and all regulatory authorities. The extension period of the study may be terminated by the sponsor for any reason.

6.2. Criteria for Treatment Discontinuation

Subjects may voluntarily withdraw their consent from the study or the investigator may terminate a subject's participation if the investigator judges that the subject can no longer fully comply with the study requirements or if any of the study procedures are deemed potentially harmful to the subject.

If any of the following criteria is met during the treatment period, the study treatment will be discontinued.

1. Subject withdraws his/her consent.
2. The development of disease progression is confirmed according to the RECIST guideline (version 1.1) that makes it inappropriate to continue with study treatment according to the investigator’s discretion or consent for continued treatment beyond RECIST confirmed disease progression is not obtained. (see Section 6.3)
3. Clinical symptoms determined to be due to disease progression that makes it inappropriate to continue with study treatment according to the investigator’s discretion or consent for continued treatment beyond clinical symptoms that are determined to be due to disease progression is not obtained. (see Section 6.3)
4. Onset of CTCAE grade ≥ 3 hypertension for which a causal relationship to the investigational product cannot be ruled out. (However, the judgment on whether or not to continue the treatment will be made by the investigator.)
5. Not having received a dose of the investigational product within the past consecutive 3 weeks for specific reasons, such as the onset of a treatment related adverse event.
6. Treatment with prohibited concomitant medication of sufficient dose and duration to confound the study results or to make continuation or restarting of treatment within 3 weeks unsafe for the patient.

7. Intolerable toxicity even after 2 dose reductions.
8. Confirmed positive pregnancy test.
9. The subject is lost to follow-up.
10. The subject is dead.
11. The investigator determines that continuation of study treatment is not appropriate.

6.3. Treatment continuation after disease progression

Patients who will be treated beyond disease progression must review and sign a supplemental informed consent form before continuing on study drug. In addition, the following activity must be performed and the investigator must provide documentation of their opinion with supporting laboratory evaluation data that:

- The patient demonstrates investigator-assessed potential for clinical benefit and does not have rapid disease progression.
- It is safe to continue study drug and the patient, by evidence of signing consent, is tolerant of any continuing adverse events.
- ECOG performance status of 0 or 1 or stable ECOG performance status of 2 with no signs of rapid deterioration (ECOG status of 2 for past three months or more where the investigator feels that the deterioration of ECOG performance status from baseline at study entry is not indicative of potential to have serious adverse events within at least 30 days from beginning of continuation study treatment).
- The patient has a life expectancy of more than 30 days.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases).
- A radiographic assessment/scan should be performed approximately 8 weeks (±7 days), or earlier if the patient is exhibiting symptoms that may indicate continued progression, after initial Investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued progressive disease. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with study therapy.

For the patients who continue receive study therapy beyond progression, further progression is defined as an additional 15% increase in tumor burden from time of initial progression. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial progression or

rapid deterioration in the performance status. Study treatment should be discontinued permanently upon documentation of further progression.

Laboratory tests will continue with other study evaluations as described in the subsequent cycle study schedule to adequately ensure subject safety and further evaluations to ensure the subjects safety and continued benefit may be performed at the investigator's discretion.

After the decision to end study treatment permanently, an end of treatment (EOT) examination will be performed (at completion/discontinuation) and the subject will proceed to the post-treatment follow-up and survival follow-up. However, subjects in either treatment group will be withdrawn from the study if they meet any of the following criteria:

1. Subject withdraws his/her consent on the follow-up period.
2. Subject is lost to follow-up.

Post-treatment follow-up can be carried out before withdrawal if the subject agrees to it. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal. When subjects withdraw from the study, they will be asked whether the study center can continue to contact them or family members for survival status only. If this consent is withdrawn, publicly accessible records may be used for documentation of death.

6.4. Handling Early Withdrawals

In any case of early withdrawal from the study, the date and reason should be recorded in the subject's eCRF and source documents. If the reason for early withdrawal was an AE, the outcome of the AE should be reported according to Section 7.2 and 7.3. All subjects who have received at least one dose of IP should complete all tests scheduled for the EOT wherever possible.

Screening numbers and randomization numbers, once allocated, cannot be reused. Any new subject will always receive new subject numbers (screening number and randomization number).

6.5. Medical Care After the End of Treatment for Withdrawn Subjects

Subjects for whom the study is terminated or suspended or who are withdrawn from the study due to disease progression or intolerable toxicity will be provided with or directed

to medical care and treatment, as deemed best for the study by the investigator.

After being withdrawn from the treatment, subjects will be monitored for survival status (See Section 3.4.5 and 3.4.6).

7. SAFETY REPORT

7.1. Definition

7.1.1. Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient 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. Treatment-emergent adverse event (TEAE) is defined as an AE that has 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. The safety analysis will be carried out with TEAE. Adverse events collected during screening period (from the time of informed consent until right before the first administration of the investigational product) will be separately listed and reviewed.

7.1.2. 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

7.2. Assessment Criteria

7.2.1. Severity Evaluation

The severity of adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 issued by National Cancer Institute (NCI) [39]. Adverse events which cannot be graded by the NCI-CTCAE version 4.03 will be classified as follows based on the maximum intensity (See Table 6).

Table 6. Definition of Severity Grade of Adverse Events

Grade	Description of Severity
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 ADL*
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
4	Life-threatening consequences; urgent intervention indicated.
5	Death Related to AE

ADL, activity of daily living

* Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking

medications, and not bedridden.

7.2.2. Causality Evaluation

The investigator should assess the causality of AEs and record the causal relationship, along with the ground that such an assessment is made on, in the eCRF. In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

The causality of AEs and SAEs to study treatment should be determined using the following definitions as guidelines[40]. AEs with at least possible relationship and AEs with conditional and unassessable relationship are considered causally related to the study treatment.

Table 7. Definition of Causality Assessment Criteria

Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable /Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)

Term	Assessment Criteria
	• Disease or other drugs provide plausible explanations
Conditional /Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable /Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

7.3. Serious Adverse Event Reporting

All SAE must be reported to the sponsor without delay from the time of investigator's acknowledgement on the event, whether or not the SAE has a causal relationship to the investigational product. The investigator is responsible for informing the IRB/IEC of the SAE, as per local requirements. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the sponsor without delay, whether or not it has a causal relationship to the investigational product. All SAE will be recorded in the eCRF. The site should fax or e-mail the SAE Report Form within 24 hours from the time of discovery of the SAE with as much information as possible to the sponsor.

During the extension period, new SAE should only be reported for subjects who are taking apatinib and have not completed Post-treatment Follow-up visit.

The SAE form should have the following information:

- Study title, protocol number, and sponsor name
- Reporter's name, investigator's name, and contact number
- Site name, site number, and subject's identification code (subject's study number)
- SAE name, start and stop dates of the event
- Causality to the investigational product, action taken in regard to investigational product, and treatments (any procedures or medications given) to manage the SAE, and the outcome of the event

If the site obtains additional information regarding the event after submitting the Initial SAE Report Form, the site should prepare a Follow-up SAE Report Form and send it to

the sponsor through fax or e-mail. Only new or corrected information should be added to the Follow-up SAE Report Form, along with identifying information regarding the subject and the event. All AE other than SAE, will be reported on the AE page of the eCRF.

The contact information for SAE reporting is as follows;

Main address:

- Name: LSK Global PS, PV department
- Email: [redacted]
- Fax Number: [redacted]

Sub address for Japan patients only (cc):

- Name: Department of Pharmacovigilance, Mediscience Planning Inc.
- Email: [redacted]
- Fax: [redacted]

7.4. Exposure During Pregnancy

Apatinib is not intended for use during pregnancy or lactation. Reproductive studies in animals have not been performed to date with Apatinib and there have been no data regarding the exposure during human pregnancy. Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of Apatinib is likely to result in adverse effects on pregnancy. If a potential subject is a female of childbearing potential, a negative pregnancy test (urine or serum) must be obtained before she can be enrolled as a subject. A female subject or a male subject's female sexual partner must use effective contraception consistently and correctly during the study and for at least 28 days after they have stopped taking the investigational products. It is not known whether Apatinib is secreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a female subject or a male subject's female sexual partner must not breastfeed while receiving the investigational products during this study and for at least 28 days after they have stopped taking the investigational products. Nonetheless, if any pregnancy or breastfeeding occurs to a female subject or a male subject's female sexual partners, during the study period and for at least 28 days after the end of treatment, the

event must be reported to the sponsor without delay. In addition, the follow-up survey will be conducted when pregnancy occurs and the outcome of the pregnancy must be reported to the sponsor using the Pregnancy Report Form. Assessment of the event will be conducted by the investigator with consultation from sponsor and actions may be taken on a case by case basis. Potential action may include unblinding the involved subject's treatment assignment following unblinding procedure and discontinuing study treatment. Subsequent reporting of such event and the following action will be submitted to relevant ethic committee and regulatory in accordance to local regulation and standard procedures.

Please send the Pregnancy Report Form for reporting exposure during pregnancy or breastfeeding to the following e-mail, or fax if not available;

Main address:

- Name: LSK Global PS, PV department
- Email: [redacted]
- Fax Number: [redacted]

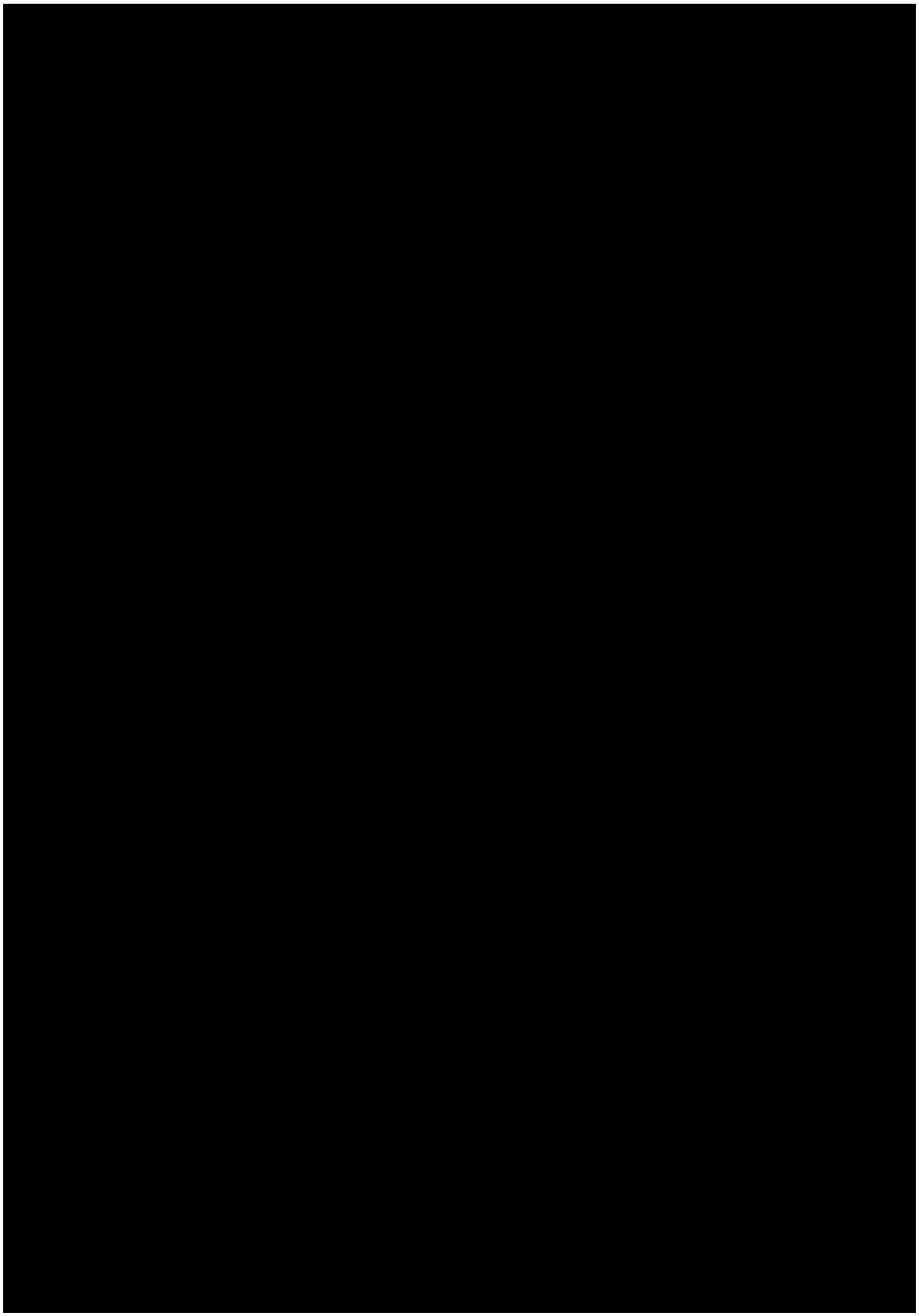
Sub address for Japan patients only (cc):

- Name: Department of Pharmacovigilance, Mediscience Planning Inc.
- Email: [redacted]
- Fax: [redacted]

8. STATISTICAL METHODS

8.1. Sample Size Calculation and Rationale

[redacted]



[redacted]

8.2. Evaluation Criteria and Methods

8.2.1. Primary Efficacy Endpoint

Overall Survival (OS): Time from randomization to death. Subjects alive or lost to follow-up at the end of study (EOS) are censored.

For the purposes of analysis, the end of study (EOS) is defined as a designated date soon after the 325th death event has been confirmed. All data prior to this date will be used for efficacy and safety analysis.

8.2.2. Secondary Efficacy Endpoints

- Progression Free Survival (PFS): Time from randomization to either radiological progression or death. Subjects alive and free of progression at the end of study (EOS) are censored.
- Objective Response Rate (ORR): Percentage 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 or partial response, or stable disease.
- Global health status/quality of life score according to European Organization 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

8.2.3. Safety Endpoints

Safety analyses will be based on the Safety Set and the assessments will be made with regard to AEs, abnormalities in laboratory tests, ECOG performance, 12-Lead ECG, physical examination and vital signs, etc.

8.2.4. Exploratory Endpoints

The relationship between efficacy measure and pharmacodynamic parameters (VEGF, sVEGFR-1, sVEGFR2 and sVEGFR3) will be explored. In addition to this, pharmacokinetic parameters (C_{max}, T_{max}, AUC, half-life, etc.) will be evaluated for apatinib.

8.3. Statistical Analysis

LSK Global Pharma Services Co., Ltd. will perform statistical analysis. Outlines of analysis are described below, and details of analysis methods will be provided in the Statistical Analysis Plan (SAP).

Version 1.0 of the SAP will be finalized before EOS.

8.3.1. General Principles of Data Analysis

Statistical analyses will be performed using SAS software (SAS Institute, SAS Circle, Cary, NC, USA) and all statistical tests, unless otherwise specified, will be two-sided at a 5% significance level.

8.3.2. Analysis Population

Data obtained from subjects in this study will be analyzed by intent to treat (ITT) set, safety set, full analysis set (FAS) or per protocol set (PPS).

- ITT set consists of data from all subjects who are randomized. In the ITT set, subjects will be included in the group to which they were 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 Apatinib 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.
- FAS consists of data from all subjects who received at least one dose of the Apatinib or placebo. The FAS will be used for all efficacy analyses.
- 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 all efficacy analyses.

8.3.3. Demographic and Baseline Characteristics

Demographic 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.

8.3.4. Primary Efficacy Analysis

The primary efficacy analysis will be conducted using the ITT set.

Overall Survival (OS): Time from randomization to death. Subjects alive or lost to follow-up at the end of study (EOS) are censored.

The comparison of OS between the two treatment groups will be performed with a stratified logrank test 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 and the randomization stratification variables as 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. $\geq 4^{th}$)].

Kaplan-Meier estimates will be calculated for each treatment group to construct the survival curve. The median overall survival and its 95% CI will also be presented.

8.3.5. Key Secondary Efficacy Analyses

If the primary analysis of OS is statistically significant, then the key secondary endpoints of PFS and ORR will be analyzed using a fixed-sequence testing procedure. These analyses will be conducted using the ITT set. First, PFS will be analyzed using the same statistical methods that are used in the primary efficacy analysis of OS. If the analysis of PFS is statistically significant, then ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. However, if a prior test is not statistically significant, then the subsequent analyses will be exploratory rather than confirmatory.

- Progression Free Survival (PFS): Time from randomization to either radiological progression (determined by the central imaging analysis facility) or death from any cause. Subjects alive and free of progression at the end of study (EOS) are censored. Options for PFS assessment for each situation are as shown in Table 7, and censoring date will be based on the last tumor assessment date.
- 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).

For PFS, the same statistical method that is used in primary efficacy analysis (OS) will be performed.

For the ORR (CR or PR), the frequency and percentage of subjects will be calculated

and the 95% confidence interval will be provided. Response in both treatment groups will be compared with the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

Table 8. PFS censoring rule (applies only disease progression documented by imaging data)

Situation	Disease progression or censoring date	Outcome
No baseline tumor assessment data	Time of enrollment	Censored
Progression documented between scheduled visits	Whichever comes first: • Date of tumor assessment indicating new lesion (disease progression based on new lesion) or • Date of last tumor assessment measuring lesions (disease progression based on the increase of total sum of lesions)	Progressed
No progression	Date of last tumor assessment of the measured lesions	Censored
Treatment discontinuation due to disease progression without documented progression	Date of last tumor assessment of the measured lesions	Censored
Treatment discontinuation due to toxicity or other reasons	Date of last tumor assessment of the measured lesions	Censored
Initiation of new anticancer therapy	Date of last tumor assessment of the measured lesions	Censored
Death before the first disease progression assessment	Date of death	Progressed
Death between appropriate assessment	Date of death	Progressed

Situation	Disease progression or censoring date	Outcome
visits		
Death or disease progression after two or more missing visits	Date of last tumor assessment of the measured lesions	Censored

8.3.6. Other Secondary Efficacy Analyses

The primary and key secondary endpoints will also be analyzed using the FAS and PP sets. All other secondary efficacy endpoints will be analyzed in the ITT, FAS, and PP sets 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, or stable disease.
- Global health status/quality of life score according to European Organization 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.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), EORTC QLQ-STO22 and EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire will be analyzed using analysis of covariance (ANCOVA) models with treatment group and the randomization stratification variables as factors, and the baseline value of the corresponding endpoint as a covariate.

8.3.7. Safety Analysis

Adverse event

Summary and analysis of adverse events will be performed for treatment-emergent adverse events. Treatment-emergent adverse events are adverse events that were absent before the drug administration but occurred after the administration, or if present at baseline worsened in severity after drug administration.

For the occurrence of treatment-emergent adverse events, the occurrence of adverse drug reactions (ADR), and the occurrence of serious adverse events (SAE), the frequency and percentage will be presented. Treatment-emergent adverse events, ADR and SAE will be coded using System Organ Class (SOC) and Preferred Term (PT) based on MedDRA and the AE severity will be classified according to NCI-CTCAE. Also, the number of subjects, incidence rate and number of incidences will be presented for the coded adverse events.

Other safety endpoints including laboratory test results and vital signs

For the analysis of safety data, including laboratory values, vital signs, physical examination, 12-lead ECG and ECOG performance status, continuous variables will be summarized using descriptive statistics (mean, median, SD, minimum and maximum) and categorical variables will be summarized using numbers and percentages of subjects. If it is necessary, a normal/abnormal shift of the safety endpoint will be summarized.

8.3.8. Exploratory Analysis

The relationship between efficacy measures and pharmacodynamic parameters (VEGF, sVEGFR-1, sVEGFR2 and sVEGFR3) will be evaluated. Detailed methodology of statistical analysis for the exploratory variables will be described in the statistical analysis plan (SAP).

In addition, detailed methodology of statistical analysis for pharmacokinetic parameters will be provided in an additional document described by the PK analysis facility.

8.3.9. Extension Period Analysis

Efficacy and safety data conducted during the extension period will be summarized descriptively. No formal statistical analyses will be conducted. Additional details concerning the extension period analyses will be provided in a separate Extension Period Statistical Analysis Plan.

8.4. Independent Data Monitoring Committee (IDMC) and Interim Analysis

8.4.1. 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 convene when approximately 163 events are observed to review

unblinded results of the interim analysis. The IDMC can also 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.

8.4.2. Interim Analysis

An interim analysis will be conducted with collected clinical data when approximately 163 (approximately 50% of the required 325 events) events are observed. All planned study procedures such as patient 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 will assess the primary efficacy endpoint. 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 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 is less than 0.2. Early stopping for futility interim analysis does not inflate the Type-I error, thus Type I-error adjustment is not needed.

9. QUALITY CONTROL AND QUALITY ASSUARANCE

9.1. Monitoring

During the study conduct, study monitors of the sponsor or designated personnel must be allowed to visit all study sites periodically to assess the data quality and study integrity and to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs is accurate. The investigator and institution will allow monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this source verification.

9.2. Audit and Inspection

The sponsor or representative may conduct audits at the trial site(s). Audits will include, but are not limited to protocol compliance, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may inspect the trial site during or after the trial. The investigator should contact the sponsor immediately if this occurs, and must fully cooperate with the inspections conducted at a reasonable time in a reasonable manner.

10. ETHICS

10.1. Institutional Review Board or Independent Ethics Committee

Before initiating the study, the investigator is responsible for ensuring that the protocol including its amendments, ICF, patient recruitment procedures (e.g. advertisements), written information to be provided to the subjects, IB, available safety information, and information about payment and compensation available to subjects have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB should be appropriately constituted and perform its functions in accordance with the principles of GCP and applicable local regulatory requirements.

10.2. Ethical Conduct of the Study

The study will be conducted in accordance with the relevant regulatory requirements, this protocol, and ethical principles that are consistent with the Good Clinical Practice (GCP) guideline developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The clinical trial will also be conducted in compliance with Declaration of Helsinki, protocol, Standard specified in the Section 3 in the Article 14 and the Section 2 in the Article 80 in Pharmaceutical Law, Notification 28 from MHLW dated March 27th, 1997 “Ordinance on the criteria for the implementation of clinical trials of the drug (GCP)”. In addition, investigational site personnel and CRO(s) will comply to their regional or country standard operating procedures and local regulatory and ethic requirements. Prior to initiation of the study, the investigator and the sponsor should obtain approval/favorable opinion from the IRB/IEC on this protocol and any further amendments, and the subject information and informed consent form.

Any suspected serious breaches must be immediately reported to the sponsor. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety of the subjects or the scientific value of the study.

Personnel involved in the study will be qualified by education, training, and experience to perform their respective tasks.

10.3. Written Informed Consent

The nature and purpose of the study should be fully explained to each patient. Written informed consent must be obtained from each patient prior to any study procedures being carried out. The Patient Information Sheet and Consent Form, advertisement flyer for recruitment, and any other documents to be handed out to the subjects should be reviewed and approved by the appropriate IRB/IEC prior to use.

For UK subjects only:

> Each patient will be given a minimum of 24 hours to ask questions regarding the trial and review the informed consent form before signing.

For all subjects:

> Only participants who understand the information in the Participant information Sheet and the Informed Consent Form will be allowed to take part in the trial. If during the course of the trial new information becomes available on the drug that is being studied, this information will be discussed with the participant and a decision will be made whether or not the participant wants to continue in the study. If the participant decides to continue in the study, he/she will be asked to sign an amended, REC approved patient information sheet and consent form.

Extension period subjects:

Subjects who are not taking study medication at the time of unblinding should be followed with their original consent in place for survival status. A separate informed consent will be required at the beginning of the extension period for each subject that is taking study medication at that time. Placebo subjects should be consented to allow for continued survival reporting and best supportive care according to standard of care. Apatinib subjects should be consented to allow for continued apatinib administration, best

supportive care, survival reporting and adverse event monitoring approximately every two weeks and tumor assessment at intervals based on standard of care intervals.

10.4. Patient Data Protection

All parties involved in the study will take utmost consideration to protect the privacy of subjects. Subject's name, address, or any identifiable data will not be present on any sponsor documents, reports, publications, or in any other disclosures, except where required by law. Subject identification codes will be used in place of subject's names to distinguish individuals on case report forms and in other data. Completed case report forms will not be used for purposes other than this study. In case of data transfer, the sponsor will maintain high standards of confidentiality and protection of subject's personal data.

10.5. Protection for Subjects After End of Study

After EOS, all subjects will be provided with or directed to medical care and treatment, as deemed best for the study by the investigator.

11. Collection and Documentation of Data

11.1. Collection of Study Data

For all subjects who provide written consent and are enrolled via the Interactive Web Response System (IWRS), the investigator (or designated personnel) will enter data into the electronic case report form (eCRF) of each subject after completion of each assessment procedure without delay. The data entered into the EDC system should be made timely, accurate and complete. The investigator or a person designated by the principal investigator will use the EDC system to enter the data into the eCRFs and to correct the data. Any data entries and corrections shall be tracked in an electronic audit trail of the EDC system that captures the history of changes, including user identifications of the persons who made corrections and the changes made. The investigator will confirm that all entries in the eCRF (including audit trails and query responses) are accurate and complete and ensure the accuracy and completeness by electronically signing the eCRF. Separate documents to guide the procedures for eCRF data entries, changes and corrections, and electronic signatures will be provided to the investigator. The investigator or designated personnel who is in charge of completing eCRF should receive appropriate training prior to use of eCRF or IWRS system and they should use the unique user account provided by the sponsor to access to this system. User accounts

must not be shared or reassigned to other individuals.

The requirements for the EDC system will conform to the guidance on EDC stipulated in the Code of Federal Regulations (CFR) Title 21, Part 11 (Guidelines for the Electronic Data Handling and Management) and any applicable local regulation.

End of Study and Extension Period Study Data

The primary EDC system will be completed with safety data through to the designated End of Study date that is determined after the study team is aware of the 325th death event. All data prior to this designated date will be made accurate and complete through normal monitoring and data cleaning practices prior to locking the primary database for analysis. SAE (until 28 days after last dose of apatinib) and survival data will continue to be gathered within this primary EDC system until a supplemental extension period EDC system is made available to the investigators before or after locking of the primary EDC system database. Survival data may continue to be allowed into the primary data set for analysis after the designated EOS date and until unblinding has occurred. Any safety data after the designated EOS date should be entered in the extension period EDC system when it becomes available.

11.2. Documentation of Study Results

All original eCRF data captured in the EDC system and their copy reproduced accurately and completely from the original data will be saved in CDs or other storage media. A copy of the completed eCRF data for their subjects will be provided to each site at the end of the study.

12. ADMINISTRATIVE INFORMATION

12.1. Patient Injury and Insurance

In general, if a patient is injured as a direct result of the investigational products, the sponsor or its contracted insurance company will pay for reasonable and necessary medical treatment for the injury. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor should comply with such laws or regulations. Where applicable, the sponsor will arrange for specific insurance coverage. If health damage occurred in patient participating the clinical trial due to the willful or gross negligence of investigator’s site, indemnification will be discussed based on the contract with the site. The indemnification for the health damage

and the payment to patients will be described in the ICF.

12.2. Confidentiality

The names of all subjects will be kept confidential. In the evaluation and documentation of the study, all subjects will be identified by the numbers assigned to them. Subject numbers will be used in the CRFs. Source documents may or may not be de-identified for inspection/monitoring, however, any documents (pathology reports, radiology reports, etc.) that are provided for the sponsors record keeping that have the subject's name on them or other subject identification will only be provided to the sponsor after the subject's name or other identification is redacted and appropriate study identification (i.e., subject number) is attached. The subjects should be informed that all study materials will be kept in strict confidence. The signed ICFs will be retained by the site personnel responsible for storing records after the EOS. By signing the protocol, the principal investigator agrees to properly obtain informed consent from the subjects participating in the study and to permit inspection as requested. The subjects shall be informed that the sponsor's representative, IRBs or other governments including Korea, U.S and EU, etc. may audit the subject's medical records for verification of collected information and any information accessed during the audit will be handled strictly confidential.

12.3. Record Retention

Essential documents should be retained until 2 years, 3 years (for Korean sites), or as long as required by local law following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years, 3 years (for Korean sites), or as long as required by local law after the investigation is discontinued and relevant regulatory agency is notified. At the end of such period, the investigator should notify the sponsor in writing of its intent to destroy all such material; however, these essential documents must not be destroyed or transferred to another location without written notification of the sponsor. The sponsor is responsible for informing the investigator or institution when these documents no longer need to be retained. If the sponsor wants these essential documents to be retained for longer than such period, such materials should be retained at the sponsor's expense.

12.4. Publication Policy

Any data from the study conducted according to this protocol are the property of the sponsor. Publication of the study data requires prior written approval of the sponsor and

will be carried out in collaboration between the investigators and the sponsor.

13. REFERENCES

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulen J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87-108.

[2] Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparties in different geographic regions of the world. *J Clin Oncol*. 2006;24(14):2137-50.

[3] Kang YK, Yoon DH, Ryoo BY, Ryu MH. Recent advances in Chemotherapy for Advanced Gastric Cancer. *Asia-Pacific J Oncol & Hematol* 2010; 2:67-74.

[4] Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol*. 2006;24(18):2903-9.

[5] Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev.* 2010;17(3):CD004064.

[6] Wesolowski R, Lee C, Kim R. Is there a role for second-line chemotherapy in advanced gastric cancer. *Lancet Oncol*. 2009; 10: 903-912.

[7] Jung JT. Chemotherapy of advanced gastric cancer. *The Korean Journal of Helicobacter and Upper Gastrointestinal Research*. 2013;13(3):142-6.

[8] Cunningham D, Starling N, Rao S, et al. Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med.* 2008;358(1):36-46.

[9] Park YH, Lee JL, Ryoo BY, et al. Capecitabine in combination with Oxaliplatin (XELOX) as a first-line therapy for advanced gastric cancer. *Cancer Chemother Pharmacol.* 2008;61(4):623-9.

[10] Kim TH, Park SR, Ryu KW, et al. Phase 3 trial of postoperative chemotherapy alone versus chemoradiation therapy in stage III-IV gastric cancer treated with R0 gastrectomy and D2 lymph node dissection. *Int J Radiat Oncol Biol Phys.* 2012;84(5):e585-92.

[11] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355(1):11-20.

[12] Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345(10):725-30.

[13] Zang DY, A New Option for Advanced Gastric Cancer-Docetaxel and Novel Oral Fluoropyrimidine Combination Chemotherapy. *J Korean Med Assoc* 2007; 50(6): 556-60.

[14] Cheung DY, Kim JK. Molecularly Targeted Therapy for Stomach Cancer. *Korean Journal of Gastroenterology*. 2013;61(3):117-27.

[15] Bang YJ, Van Cutsem E, Feyereislova A, et al. ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010;376(9242):687-97.

[16] Ferry DR, Anderson M, Beddard K, et al. A phase II study of gefitinib monotherapy in advanced esophageal adenocarcinoma: evidence of gene expression, cellular, and clinical response. *Clin Cancer Res.* 2007;13:5869-5875.

[17] Dragovich T, McCoy S, Fenoglio-Preiser CM, et al. Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. *J Clin Oncol*. 2006; 24: 4922-7.

[18] Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet*. 2013;14:490-99.

[19] Waddell T, Chau L, Cunningham D, et al. Epirubicin, oxalipaltin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol*. 2013;14:481-89.

[20] FDA.gov press release for ramucirumab approval, accessed April 22, 2014. [21] Ramucirumab gastric cancer regimen & reference.

[22] Fuchs CS, Tomasek J, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2014 Jan 4; 383 (9911):31-9.

[23] Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advaned gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-bline, randomised phase 3 trial. *Lancet Oncol*. 2014 Oct;15(11):1224-35.

[24] Ohtsu A, Shah MA, Cutsem EV, et al., Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a ranomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011;29(30):3968-76.

[25] Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007;356: 125–13.

[26] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359: 378–390.

[27] Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet.* 2006;368:1329–1338.

[28] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA . Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007; 356:115–124.

[29] Bang YJ, et al. Phase II Study of sunitinib as second-line treatment for advanced gastric cancer. *Invest New Drugs*. 2011;29:1449-58.

[30] Jin Li, Xinmin Zhao, et al. Safety and pharmacokinetics of novel selective vascular endothelial growth factor receptor-2 inhibitor YN968D1 in patients with advanced malignancies. *BMC Cancer*. 2010;50:529.

[31] Jin Li, Qin S, Xu J, et al. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol*. 2013 Sep 10;31 (26):3219-25.

[32] 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.

[33] EORTC QLQ-C30 Scoring Manual, EORTC Quality of Life Group, 2001.

[34] Guidelines for assessing Quality of Life in EORTC clinical trials, EORTC Quality of Life, 2002.

[35] Lim HS, Cho GS, Park YH, Kim SK. Comparison of quality of life and nutritional status in gastric cancer patients undergoing gastrectomies. *Clin Nutr Res.* 2015;4:153-9.

[36] Yun YH1, Park YS, Lee ES, et al., Validation of the Korean version of the EORTC QLQ-C30, *Qual Life Res*. 2004 May;13(4):863-8.

[37] Janssen MF1, Pickard AS, Golicki D, et al., Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study, *Qual Life Res*. 2013 Sep;22(7):1717-27.

[38] Kim SH, Hwang JS, Kim TW, et al., Validity and reliability of the EQ-5D for cancer patients in Korea, *Support Care Cancer*. 2012 Dec;20(12):3155-60.

[39] NCI CTCAE version 4.03.http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

[40] The use of the WHO-UMC system for standardised case causality assessment. http://www.who-umc.org/Graphics/26649.pdf. The Uppsala monitoring centre.

14. APPENDICES

Appendix 1: Eastern Cooperative Oncology Group (ECOG) Performance Status

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.

Appendix 2: Tumor Response Criteria

Tumor assessment will be performed based on the revised RECIST guideline (version 1.1)
[Reference: Eisenhauer EA, Therasse P, Bogaerts J, et al., New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), European Journal of Cancer 2009;45:228-247]

1. Baseline assessment

The baseline tumor lesions assessed within 14 days before randomization will be categorized as measurable lesions (lesions that can be accurately measured in at least one dimension as ≥10 mm) or as non-measurable lesions (all other lesions, including lesions <10mm in longest diameter, infiltrating type of GC, and truly non-measurable lesions). Specific criteria for determination for measurability will be provided in a separate imaging guideline.
All measurable lesions should be identified as target lesions, and should be evaluated by measurement of the sum of the longest diameters of measurable and viable lesions.

2. Definitions

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

- 10 mm by CT/MRI scan (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

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

Target lesions: All measurable lesions up to a maximum of five lesions in total and two lesions per organ with the greatest size (a long axis for non-nodal lesions and a short axis for nodal lesions) should be identified as target lesions. Target lesions should be representative of all involved organs and in addition be those that lend themselves to reproducible repeated measurements (with large lesions that are difficult to measure avoided).

Non-target lesions: All lesions not selected as target lesions will be handled as non-target lesions, regardless of whether measurement is possible. Multiple non-target lesions in the same organ or site may be recorded as a single item (e.g., multiple enlarged pelvic lymph

nodes, multiple liver metastases).

3. Response criteria

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 diameter while on study.
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).

Table 3. Time Point Response

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

Table 4. Best Overall Response When Confirmation Of CR And PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

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