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.

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.

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

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)

	• 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

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

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

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.

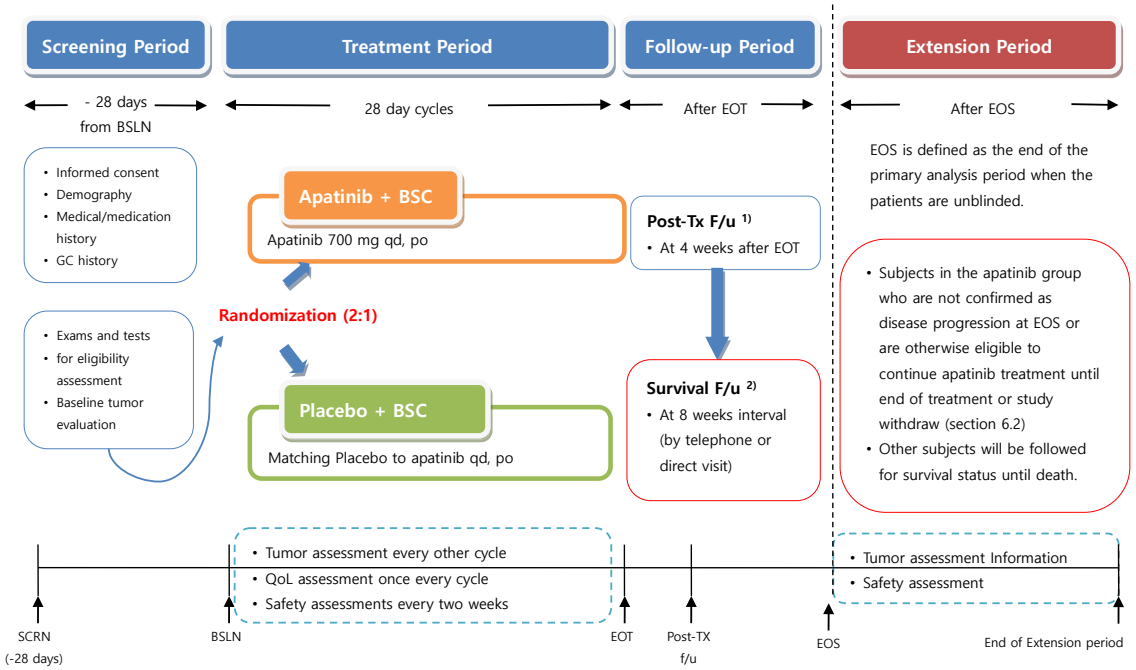

Figure 1. Study Scheme

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.

- 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

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.

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.

- 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

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

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.

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).

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.

TABLE OF CONTENTS

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).

	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

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

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

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

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

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

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.

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]

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

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