Supplementary Material

1. Clinical trial sites and investigators

Clinical trial site	Principal investigators
Asan Medical Center; Seoul, South Korea	Yoon-Koo Kang, MD, PhD (Parts 1-3)
Huntsman Cancer Institute; Salt Lake City, Utah, USA	Sunil Sharma, MD (Parts 1-2) Theresa Werner, MD (Parts 1-2)

2. Eligibility criteria

1) Parts 1 and 2

(1) Inclusion criteria

① 18 years of age or older

② Patients may have been enrolled with the following malignancies:

Part 1: Patients with any solid malignant tumor that was refractory to conventional therapy or the patient did not tolerate the conventional therapy

Part 2: Patients diagnosed with non–small cell lung cancer, colorectal cancer, hepatocellular carcinoma, gastric cancer, neuroendocrine tumor or mesothelioma that was refractory to conventional therapy or the patient did not tolerate the conventional therapy

③ Measurable disease defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as measured by a suitable radiographic technique

④ Life expectancy ≥ 3 months

⑤ Patient had to be suitable for oral administration of study drug

⑥ Signed written informed consent was obtained

⑦ Adequate bone marrow, renal and liver function as manifested by the following:

a. Complete blood count (CBC): absolute neutrophil count ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, hemoglobin ≥ 9.0 g/dL

b. Comprehensive metabolic panel (CMP): Creatinine clearance > 50 mL/min or serum creatinine < 1.5×upper limit of normal (ULN), serum bilirubin < 2.5×ULN, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5.0×ULN

c. Coagulation profile with prothrombin time (PT) and international normalized ratio (INR), each ≤ 1.5×ULN

d. Proteinuria < 200 mg by 24-hour urine collection without evidence of active sediment or clinically significant hematuria

⑧ Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

⑨ Female patients of child-bearing potential agreed to use contraceptive measures starting 1 week before the administration of the first dose of YN968D1 until 4 weeks after discontinuing study drug and male patients agreed to use contraceptive measures during the study and ending 4 weeks after last dose of study drug

⑩ Female patients of child-bearing potential were confirmed to have either a negative serum beta-human chorionic gonadotropin (β-hCG) test or had been evaluated by a gynecologist to confirm the patient is not pregnant, within 7 days prior to administration of initial dose of YN968D1

⑪ Ability and willingness to comply with the study protocol for the duration of the study and with follow-up procedures

(2) Exclusion criteria

① Women who were pregnant or lactating

② Therapy with clinically significant systemic anticoagulant or antithrombotic agents within 7 days prior to the first scheduled dose of YN968D1 that may have prevented clotting and, in the opinion of the Investigator, would have placed the patient at risk

③ Hemoptysis within 3 months prior to first scheduled dose of YN968D1

④ Cytotoxic chemotherapy, immunotherapy, radiotherapy or other targeted therapies within 4 weeks (6 weeks in cases of mitomycin C, nitrosourea, lomustine) prior to first scheduled dose of YN968D1

⑤ Surgery or visceral (e.g., hepatic or renal) biopsy within 28 days prior to first scheduled dose of YN968D1

⑥ Minor surgical procedure performed within 7 days prior to first scheduled dose of YN968D1

⑦ Prior exposure to YN968D1 (prior treatment with an angiogenesis inhibitor was not exclusionary)

⑧ Concomitant treatment with strong inhibitors or inducers of CYP3A4, CYP2C9 and CYP2C19

⑨ Known history of human immunodeficiency virus infection

⑩ Patients with active bacterial infections and/or who were receiving systemic antibiotics

⑪ Current or past diagnosis of leukemia within the past 5 years

⑫ Prior radiotherapy at the target lesion

⑬ Known central nervous system (CNS) metastases or clinical evidence of CNS involvement that was not stable for the last 3 months by radiology documentation

⑭ Medical history of non-healing wound within past 2 weeks

⑮ History of bleeding diathesis or bleeding within 14 days prior to enrollment

⑯ Medical history of clinically significant thrombosis (bleeding or clotting disorder) within the past 3 months that, in the opinion of the Investigator, may have placed the patient at risk of AEs on an anti-angiogenesis product

⑰ History of non-malignant gastrointestinal bleeding, gastric stress ulcerations or peptic ulcer disease within the past 3 months that, in the opinion of the Investigator, may have placed the patient at risk of AEs on an anti-angiogenesis product

⑱ History of idiopathic or hereditary angioedema

⑲ History of sickle cell or any hemolytic anemia

⑳ History of uncontrolled hypertension that, in the opinion of the Investigator, was not well-managed by medication and may have placed the patient at risk when taking a vascular endothelial growth factor (VEGF) inhibitor

㉑ Complete left bundle branch block, bifascicular block (right bundle branch block with either left anterior hemiblock or left posterior hemiblock)

㉒ Any clinically significant ST segment and/or T-wave abnormalities

㉓ Presence of unstable atrial fibrillation (ventricular response rate > 100 beats per minute). Patients with stable atrial fibrillation were allowed in the study provided they did not meet another exclusion criteria

㉔ Myocardial infarction or unstable angina pectoris within 6 months prior to starting study drug

㉕ Congestive heart failure (New York Heart Association Class III-IV)

㉖ History of other significant cardiovascular disease or vascular disease within the last 6 months (e.g. such as hypertensive crisis, hypertensive encephalopathy, stroke or transient ischemic attack or significant peripheral vascular disease) that, in the opinion of the Investigator, may have placed the patient at risk when taking a VEGF inhibitor

㉗ QT interval corrected using Fridericia's formula (QTcF) based on the average of three electrocardiogram (ECG) measurements at the screening visit:
US site: > 450 msec for male patient or > 470 msec for female patients,
Korean site: > 450 msec for male patient or > 450 msec for female patients.

㉘ Baseline echocardiogram (within 2 months) with left ventricular ejection fraction (LVEF) < 50%

㉙ History of clinically significant glomerulonephritis, biopsy proven tubulointerstitial nephritis, crystal nephropathy or other signs of renal insufficiency

㉚ Treatment with an investigational agent within the longest time frame of either 5 half-lives or 30 days of initiating study drug

㉛ Medical or psychiatric illness that, in the opinion of the Investigator, may have impacted the safety of the patient or objectives of the study

㉜ Known recreational substance use or psychiatric illness that, in the opinion of the Investigator, may have affected compliance with scheduled visits

㉝ Known hypersensitivity to YN968D1 or components of the formulation

2) Part 3

(1) Inclusion criteria

① Patients over 19 years old

② Patients with histologically proven adenocarcinoma of stomach or gastric junction

③ Unresectable or distant metastases and relapsed patients

④ Patients who failed in or showed no response to the current standard treatment with no alternative medications

⑤ Patients with measurable disease as defined by RECIST 1.1 measured by appropriate imaging methods

⑥ Patients whose life expectancy is more than 3 months

⑦ Patients who can swallow investigational new drug tablets

⑧ Patients who can submit a written consent prior to initiation of clinical trial

⑨ Patients with appropriate bone marrow, kidney, and liver function that meet the following criteria:

CBC: Absolute neutrophil count $\geq$ 1500/mm^3, platelets $\geq$ 100,000/mm^3, hemoglobin $\geq$ 9.0 g/dL

Blood coagulation test: PT and INR, respectively $\leq$ 1.5×ULN

CMP: Creatinine clearance > 50 mL/min or serum creatinine < 1.5×ULN, serum bilirubin < 2. ×ULN, AST and ALT $\leq$ 5.0×ULN

⑩ ECOG performance status $\leq$ 2

⑪ For female subjects, patients who had undergone surgical sterilization (hysterectomy or bilateral tubal ligation) or is menopause, or fertile female patients whose serum β-hCG was negative within 7 days prior to the first dose

⑫ Male and female subjects of child-bearing potential who can use an effective method of contraception

⑬ Patients who are able and willing to follow the protocol during the study and the follow-up procedures

(2) Exclusion riteria

① Pregnant or lactating female patients

② Patients undergoing clinically significant systemic anticoagulant or antithrombin agents treatment that can interfere with blood coagulation and put the patients in danger within 7 days prior to administration of Apatinib Mesylate (YN968D1)

③ Patients with a history of hemoptysis within 3 months prior to administration of Apatinib Mesylate (YN968D1)

④ Patients who received cytotoxic chemotherapy, immunotherapy, radiotherapy or other target therapy within 4 weeks (6 weeks for mitomycin C, nitrosourea, lomustine) prior to administration of Apatinib Mesylate (YN968D1)

⑤ Patients who underwent surgery or internal (e.g., liver or kidney) biopsy within 28 days prior to administration of Apatinib Mesylate (YN968D1)

⑥ Patients who underwent minor surgery within 7 days prior to administration of Apatinib Mesylate (YN968D1)

⑦ Patients who previously had treatment with Apatinib Mesylate (YN968D1)

⑧ Patients in need of concurrent treatment with strong inhibitors or inducers of CYP3A4, CYP2C9 and CYP2C19

⑨ Patients with HIV infection or past history of HIV

⑩ Patients receiving active bacterial infections and/or systemic antibiotics

⑪ Patients diagnosed with other cancers within the past 5 years

⑫ Patients who received radiation treatment for target lesions within 28 days prior to administration of Apatinib Mesylate (YN968D1) or who received radiotherapy at other sites within 14 days prior to administration

⑬ Patients who had clinical evidence of CNS metastasis known by radiologic records or unstable CNS invasion for the past 3 months

⑭ Patients with a history of non-healing wounds within the past 2 weeks

⑮ Patients with a history of bleeding tendency or bleeding within 14 days prior to enrollment

⑯ Patients with a history of clinically significant embolism (hemorrhage or coagulation disorder) within the last 3 months that can cause risk of adverse reactions to anti-angiogenesis agent to the subject, as judged by the investigator

⑰ Patients with a history of non-malignant gastrointestinal bleeding, stress stomach ulcer or peptic ulcer disease within the past 3 months that can cause risk of adverse reactions to anti-angiogenesis agent to the subject, as judged by the investigator

⑱ Patients with a history of idiopathic or hereditary angioedema, a history of sickle cell or other hemolytic anemia

⑲ Patients with a history of uncontrolled hypertension which is not well controlled by medication and may endanger the patient when administered with VEGF inhibitors, as judged by the investigator

⑳ Patients with complete left bundle branch block, bifascicular block (right bundle branch block and left anterior or posterior hemiblock)

㉑ Patients with clinically significant ST segment or T wave abnormality

㉒ Patients with unstable atrial fibrillation (ventricular response>100/min) (patients with stable atrial fibrillation may participate if they do not meet other exclusion criteria)

㉓ Patients who had abnormal electrocardiograms or LVEF during the past 3 months, as judged by the investigator

㉔ Patients with symptoms of myocardial infarction or unstable angina pectoris within 6 months prior to the start of the test drug

㉕ Patients with congestive heart failure (New York Heart Association class III-IV)

㉖ Patients with a history of other significant cardiovascular or vascular disease within the past 6 months (e.g. hypertensive crisis, hypertensive encephalopathy, stroke or transient ischemic attack (TIA), or significant peripheral vascular disease) that may endanger the patient when administered with VEGF inhibitors, as judged by the investigator

㉗ Patients with a history of clinically significant glomerulonephritis, biopsy proven tubulointerstitial nephritis, crystal nephropathy, and other renal failure

㉘ Patients who did not have more than 5 times the half-life of other investigational product or have not passed 30 days before the start of the test

㉙ Patients with a medical or psychiatric illness that may affect the safety of the subject or the objective of the study, as judged by the investigator

㉚ Patients with hypersensitivity reactions to investigational drug or to formulation components of the study