Protocol 05 I4T-MC-JVCZ

Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination with Paclitaxel in Second-Line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma

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Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination with Paclitaxel in Second-Line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma

Confidential Information

Ramucirumab (LY3009806)

An open-label, randomized Phase 2 study comparing alternative ramucirumab dose in combination with paclitaxel in approximately 240 patients with metastatic or locally advanced gastric or gastroesophageal junction adenocarcinoma with disease progression during or following prior combination chemotherapy. Treatment will continue until a discontinuation criterion is met.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 07-May-2015 GMT

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1. Synopsis

Title of Study:

Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination with Paclitaxel in Second-Line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma

Summary of Study Design:

Study I4T-MC-JVCZ is a multicenter, open-label, randomized Phase 2 study comparing alternative ramucirumab doses in combination with paclitaxel in patients with metastatic or locally advanced unresectable gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression during or after prior platinum and/or fluoropyrimidine-containing combination chemotherapy.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
• Evaluate the efficacy of ramucirumab 12 mg/kg versus placebo, both in combination with paclitaxel, in terms of PFS	• PFS, as determined by investigator assessment per RECIST 1.1
Secondary	
• Evaluate the efficacy of ramucirumab 12 mg/kg versus ramucirumab 8 mg/kg, both in combination with paclitaxel, in terms of PFS	• PFS, as determined by investigator assessment per RECIST 1.1
• PK of ramucirumab in combination with paclitaxel • Safety and tolerability • ORR • DCR • Immunogenicity	• Minimum ramucirumab concentration in serum The safety endpoints evaluated will include but are not limited to the following: • TEAEs, AESIs, SAEs, and hospitalizations • Clinical laboratory tests, vital signs, and physical examinations • ORR • DCR • Blood samples for immunogenicity testing will be collected to determine antibody production against ramucirumab.
Exploratory	
• OS • Assess the relationship between biomarkers and clinical outcome	• OS • Biomarker research on genetic and circulating factors may be assessed from whole blood and plasma samples, unless precluded by local regulations.

Abbreviations: AESIs = adverse events of special interest; DCR = disease control rate; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

Treatment Arms and Duration:

		Dose and Schedule (q 28 Days)		
Arm	**N**	**Ramucirumab D1 and D15**	**Paclitaxel D1, D8, and D15**	**Number of Cycles**
1	120	8 mg/kg	80 mg/m^2	Treatment will continue until a discontinuation criterion is met.
2	120	12 mg/kg	80 mg/m^2	

Abbreviations: D = day; N = number of randomized patients; q = every.

If, at any time during the study, Lilly determines that the safety profile of ramucirumab 12 mg/kg is unacceptable, enrollment in Arms 1 and 2 will be stopped, and 30 additional patients will be enrolled in a new treatment arm (Arm 3). Patients enrolled in Arm 3 will receive ramucirumab 10 mg/kg on Days 1 and 15 in combination with paclitaxel 80 mg/m^2 on Days 1, 8, and 15, every 28 days. For ongoing patients receiving ramucirumab 12 mg/kg, dose reduction to ramucirumab 10 mg/kg is recommended; however, if the patient is receiving ramucirumab without unacceptable toxicity, the patient may continue to receive ramucirumab 12 mg/kg at the discretion of the investigator.

Analysis:

Efficacy

- Median progression-free survival (PFS) with the 95% confidence interval (CI) and PFS curves will be provided using the Kaplan-Meier method (Kaplan and Meier 1958).
- The objective response rate (ORR) with 95% CI will be summarized for each treatment arm.
- Median overall survival (OS) with the 95% CI and OS curves for each treatment arm will be provided using the Kaplan-Meier method.

Pharmacokinetics

- All concentrations will be summarized by descriptive statistics. Additional analysis utilizing the population pharmacokinetic approach may also be conducted if deemed appropriate.
- The relationship between ramucirumab exposure and selected efficacy and safety outcomes may be explored.

Safety

- Adverse events (AEs) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class/Preferred Term (PT), classified from verbatim terms. The incidence and percentage of patients with at least one occurrence of a PT will be included in the summaries, according to the most severe Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 grade (NCI 2009). Causality (relationship to study treatment), action taken, and outcome will be summarized separately. Duration of AEs will be determined and included in the listings.

- Exposure to study treatment will be summarized for each treatment arm with the following variables: number of infusions, number of cycles, duration of therapy, cumulative dose, dose intensity, and relative dose intensity.
- Laboratory results will be classified according to CTCAE Version 4.0 grade. The incidence of laboratory abnormalities will be summarized.

Immunogenicity

- The number and percentage of patients with positive anti-ramucirumab antibodies will be summarized. Any relationship with the occurrence of an infusion-related reaction and positive anti-ramucirumab antibodies may be explored.

2. Introduction

Ramucirumab (Cyramza®), a human immunoglobulin, subclass 1 anti-vascular endothelial growth factor (VEGF) Receptor 2 monoclonal antibody, obtained marketing authorization in the United States and in the European Union for the treatment of adult patients with advanced gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma with disease progression after prior platinum and/or fluoropyrimidine chemotherapy. The approvals were based on the clinical efficacy and safety demonstrated in 2 global, randomized, double-blind and placebo-controlled Phase 3 studies, RAINBOW (Wilke et al. 2014) and REGARD (Fuchs et al. 2014). RAINBOW evaluated ramucirumab in combination with paclitaxel for advanced gastric or GEJ adenocarcinoma after prior chemotherapy; REGARD evaluated ramucirumab as a single agent in the same setting.

- FDA approval was granted in April 2014 for ramucirumab as a single agent and in November 2014 in combination with paclitaxel.
- European Commission marketing authorisation was granted in December 2014 for ramucirumab in combination with paclitaxel and as monotherapy for adult patients for whom treatment in combination with paclitaxel is not appropriate.

In the Phase 1 dose-escalation study, Study I4T-IE-JVBM, weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated, and the maximum-tolerated dose was identified as 13 mg/kg when given once weekly (Spratlin et al. 2010). The dosing regimen of 8 mg/kg administered once every 2 weeks was suggested for evaluation in further trials because clearance at this dose seemed to be saturated, and trough levels were >18 μg/mL, the level at which activity was seen in mouse xenograft models treated with a ramucirumab surrogate antibody. This dosing regimen of ramucirumab 8 mg/kg every 2 weeks was used in REGARD and RAINBOW.

Both REGARD and RAINBOW confirmed that the ramucirumab dosing regimen of 8 mg/kg administered once every 2 weeks (hereafter referred to as the standard dose regimen) is a pharmacologically and clinically effective and safe dose for the treatment of patients with advanced gastric cancer and offers a favorable benefit-risk profile for these patients.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the efficacy of ramucirumab 12 mg/kg versus placebo, both in combination with paclitaxel, in terms of PFS	• PFS, as determined by investigator assessment per RECIST 1.1
Secondary	
• Evaluate the efficacy of ramucirumab 12 mg/kg versus ramucirumab 8 mg/kg, both in combination with paclitaxel, in terms of PFS	• PFS, as determined by investigator assessment per RECIST 1.1
• PK of ramucirumab in combination with paclitaxel • Safety and tolerability • ORR • DCR • Immunogenicity	• Minimum ramucirumab concentration in serum The safety endpoints evaluated will include but are not limited to the following: • TEAEs, AESIs, SAEs, and hospitalizations • Clinical laboratory tests, vital signs, and physical examinations • ORR • DCR • Blood samples for immunogenicity testing will be collected to determine antibody production against ramucirumab.
Exploratory	
• OS • Assess the relationship between biomarkers and clinical outcome	• OS • Biomarker research on genetic and circulating factors may be assessed from whole blood and plasma samples, unless precluded by local regulations.

Abbreviations: AESIs = adverse events of special interest; DCR = disease control rate; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

4. Study Design

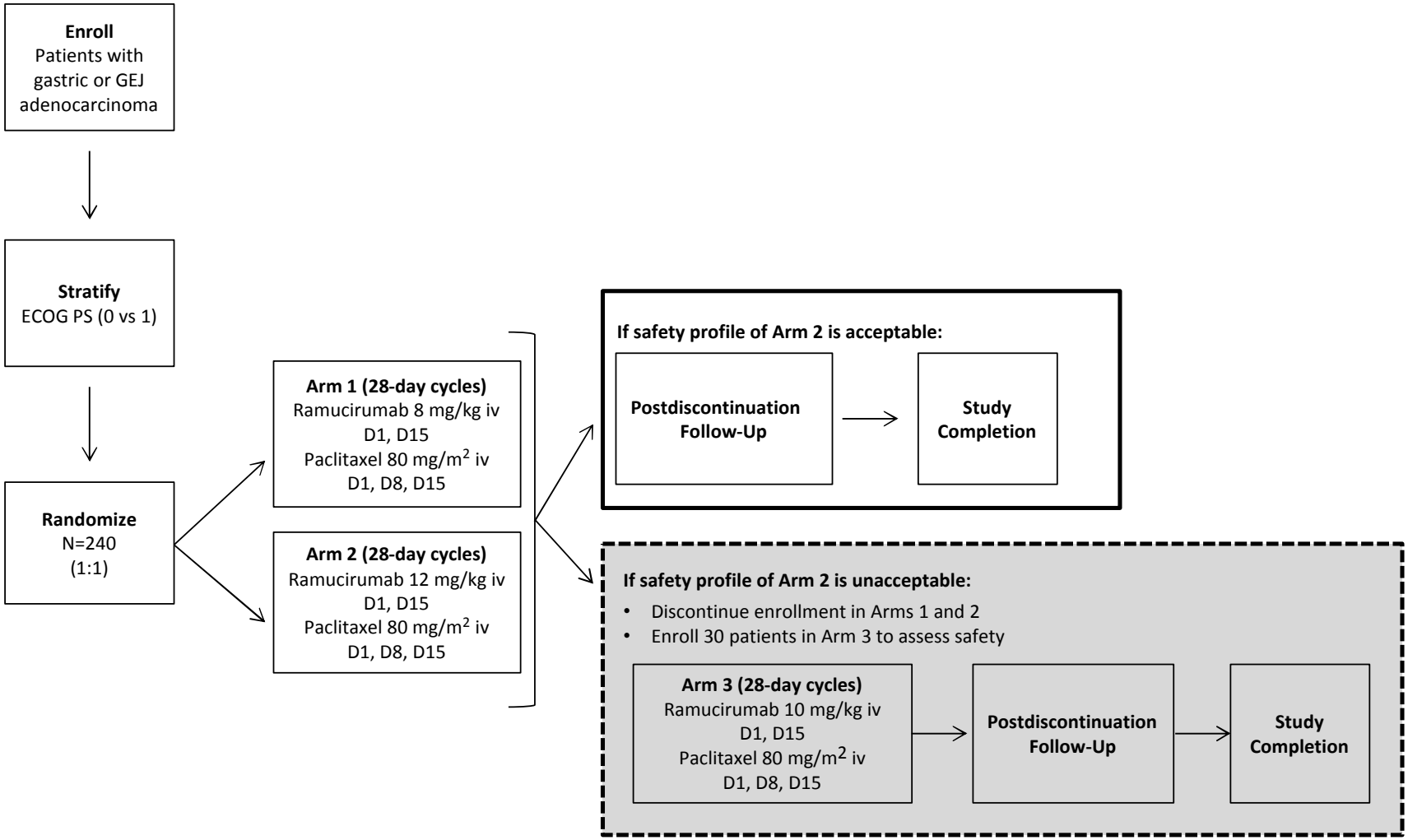
4.1. Overview of Study Design

Study I4T-MC-JVCZ (JVCZ) is a multicenter, randomized, open-label, parallel trial in patients with metastatic or locally advanced gastric cancer or GEJ adenocarcinoma (hereafter referred to as *gastric cancer*) whose disease has progressed during or following prior combination chemotherapy. The study will randomize (1:1) approximately 240 patients to the 2 treatment arms (Table JVCZ.1). Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

The primary objective of the study is to evaluate the efficacy of ramucirumab 12 mg/kg in combination with paclitaxel as determined by improvement in progression-free survival (PFS) compared with placebo in combination with paclitaxel. A key secondary objective is to evaluate the efficacy of ramucirumab 12 mg/kg versus ramucirumab 8 mg/kg, both in combination with paclitaxel, in terms of PFS. In order to perform the network analysis to compare ramucirumab 12 mg/kg versus placebo, additional data on placebo and ramucirumab 8 mg/kg, in combination with paclitaxel, from the RAINBOW study will be utilized.

If, at any time during the study, Lilly determines that the safety profile of ramucirumab 12 mg/kg (Arm 2) is unacceptable, enrollment in Arms 1 and 2 will be stopped, and 30 additional patients will be enrolled to a new treatment arm (Arm 3). For additional details, see Section 6.1.

Figure JVCZ.1 illustrates the study design.



Abbreviations: D = day; ECOG PS = Eastern Cooperative Oncology Group performance status; GEJ = gastroesophageal junction; iv = intravenous; N = number of randomized patients.

Figure JVCZ.1. Illustration of study design.

Terms used to describe the periods during the study are defined below:

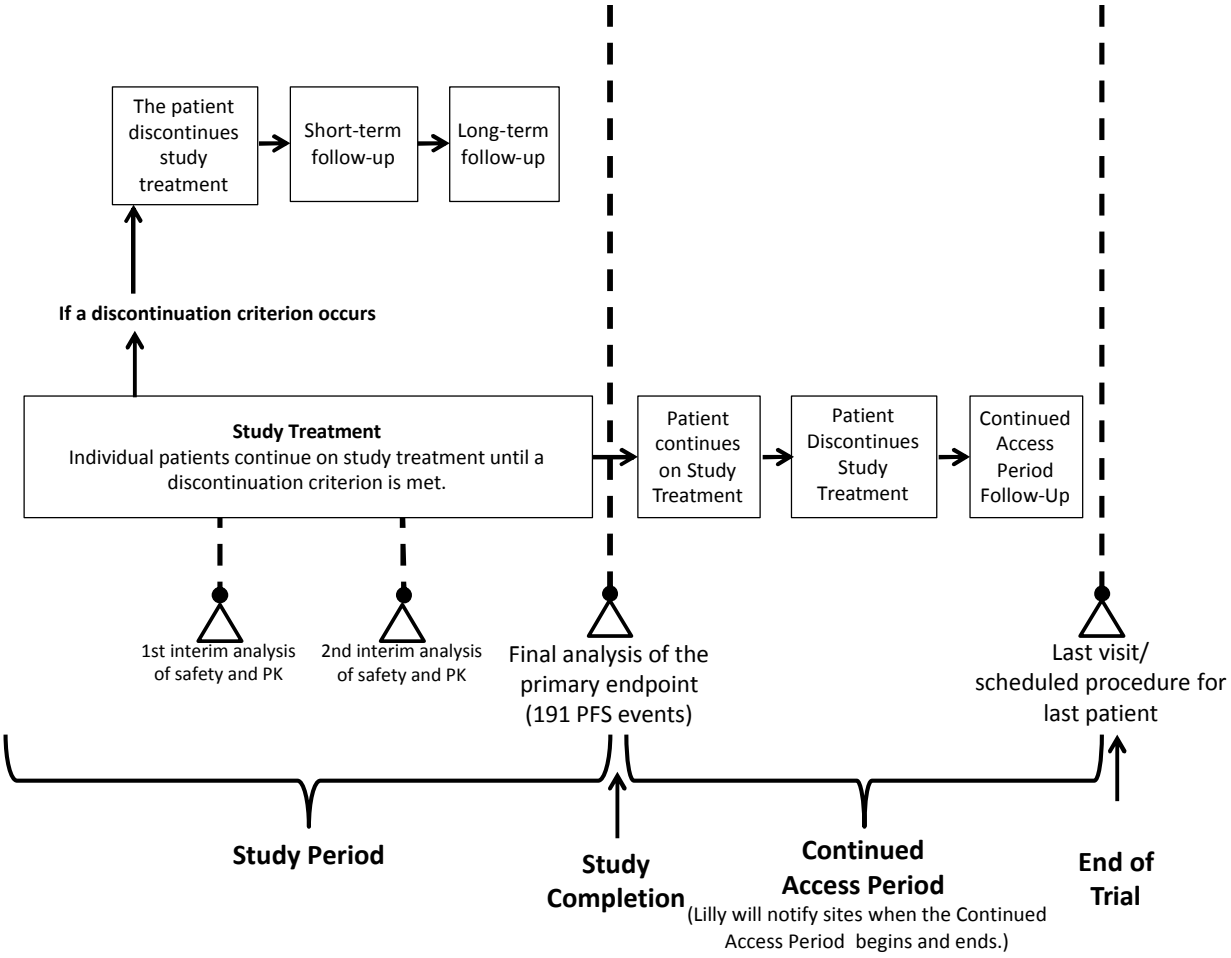
- **Baseline:** begins when the informed consent form (ICF) is signed and ends on the day before the first dose of study treatment (or at discontinuation, if no treatment is given). Patients must be randomized to treatment within 21 days after signing the ICF, and the first treatment will be administered within 7 days after randomization.
- **Study Period:** includes the Study Treatment Period and Postdiscontinuation Follow-Up. The study period does not include the continued access period.
    - **Study Treatment Period:** begins on the date of the first dose of study treatment (within 7 days after randomization) and ends on the date the patient and the investigator agree that the patient will no longer continue study treatment. The date of this agreement is to be reported on the case report form (CRF) as the *Date of Discontinuation* from study treatment.
    - **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.

      Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts until the short-term follow-up visit is completed, approximately 30 days (±7 days) after the date of discontinuation.

      Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion, whichever is earlier.

- **Continued Access Period:** begins after study completion and ends at the end of trial (see Section 4.4). During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met. The continued access period includes continued access follow-up.
    - ***Continued access follow-up*** begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days (±7 days).

Figure JVCZ.2 presents a diagram of the study period and the continued access period.



Abbreviations: PFS = progression-free survival; PK =pharmacokinetics.

Figure JVCZ.2. Study period and continued access diagram.

4.2. Rationale for Study Design

Study JVCZ is a postmarketing commitment to FDA to determine whether a higher dose of ramucirumab, in combination with paclitaxel, provides superior PFS as compared with the recommended ramucirumab dose (8 mg/kg) in combination with paclitaxel, in patients with previously treated gastric cancer.

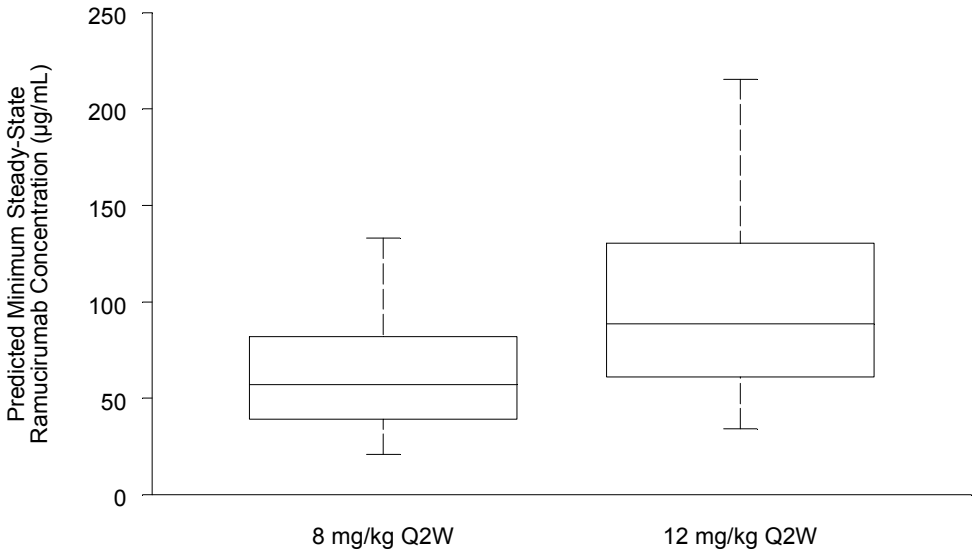
This study is designed to evaluate efficacy and safety of a higher ramucirumab dose, 12 mg/kg administered on Days 1 and 15, in combination with paclitaxel (80 mg/m^2) administered on Days 1, 8, and 15, of a 28-day cycle.

The exposure-efficacy analyses from REGARD and RAINBOW indicated an association between efficacy and ramucirumab exposure. Although exposure-safety analyses in RAINBOW also suggested that increasing exposure of ramucirumab (when given in combination with paclitaxel) is associated with increased risk of Grade ≥3 hypertension, neutropenia, and leukopenia, the association of neutropenia with ramucirumab exposure does not appear to translate to an increased risk of febrile neutropenia.

Additionally, the overall favorable safety profile of ramucirumab and the exposure-efficacy relationship observed in REGARD and RAINBOW suggested that there may be an opportunity to further improve efficacy while maintaining an acceptable safety profile in this combination therapy setting.

Study JVCZ will compare the standard ramucirumab dose (8 mg/kg) and a new, higher ramucirumab dose (12 mg/kg), both administered on Days 1 and 15, in combination with paclitaxel (80 mg/m^2) administered on Days 1, 8, and 15, of a 28-day cycle (see Table JVCZ.1) in order to examine the potential improvement in efficacy as measured by PFS.

The new ramucirumab dosing regimen (12 mg/kg) is predicted to produce approximately 50% higher exposure relative to the 8-mg/kg standard dose based on linear pharmacokinetic (PK) assumption (Figure JVCZ.3) and therefore is expected to improve PFS. However, it is unknown whether doses leading to exposures higher than the standard ramucirumab 8-mg/kg every-2-week regimen will have an acceptable toxicity profile. This study will also evaluate the safety and tolerability of the higher ramucirumab dose and assess whether higher ramucirumab exposure can still maintain an acceptable toxicity profile when given in combination with paclitaxel.



Abbreviations: $C_{min,ss}$ = minimum concentration at steady state; Q = every; W = week. Box plots depict the 5th, 25th, 50th, 75th, and 95th percentiles calculated from 1000 simulation iterations.

Figure JVCZ.3. Predicted $C_{min,ss}$ following different dose regimens.

4.3. Benefit/Risk Assessment

Information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of ramucirumab, including in ramucirumab administered in combination with paclitaxel, may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to ramucirumab may be found in Section 7 (Development Core Safety Information) of the

IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by Lilly in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

See Section 8.2.1.1 for information about adverse events of special interest (AESIs) for ramucirumab.

In countries where ramucirumab is approved, refer to the package insert for more detailed information about the known and expected benefits and risks of ramucirumab.

Refer to the paclitaxel package insert for more detailed information about the known and expected safety and risks of paclitaxel.

4.4. Study Completion and End of Trial

Study completion will occur following the final analysis of PFS, as determined by Lilly. If the study is stopped early because of safety concerns, study completion will occur following the final analysis of safety. Investigators will continue to follow the *Time and Events Table* (Attachment 1) for all patients until notified by Lilly that study completion has occurred. If Arm 3 is initiated, the study will be considered complete when patients on Arm 3 complete at least 3 cycles of therapy or discontinue treatment, whichever comes first.

"End of trial" refers to the date of the last visit or last scheduled procedure for the last patient (including patients participating in the continued access period). The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed the final follow-up visit (including the final follow-up visit for the continued access period, if applicable) or has been declared lost to follow-up.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] The patient has a histopathologically or cytologically confirmed diagnosis of gastric or GEJ (Siewert Types I-III) adenocarcinoma.

[2] The patient has documented disease progression during or within 4 months after the last dose of first-line chemotherapy for metastatic disease, or during or within 6 months after the last dose of neoadjuvant or adjuvant therapy.

a. Elevations in carcinoembryonic antigen or other tumor markers without radiographic evidence of progression do not constitute satisfactory evidence of progression on prior therapy.

b. Patients who are intolerant to first-line chemotherapy regimens are eligible, provided disease progression was assessed within 4 months after the last dose of first-line therapy.

[3] The patient received combination chemotherapy prior to disease progression.

a. Prior chemotherapy regimens must include a platinum and/or a fluoropyrimidine component and must not include a taxane or antiangiogenic agent (either approved or experimental treatment). Exposure to antineoplastic therapy, in addition to platinums and/or fluoropyrimidines, is acceptable if the agents were used in the first-line metastatic or neoadjuvant/adjuvant setting.

b. Patients who have had one or more components of first-line chemotherapy discontinued because of toxicity, but continued to receive the other component(s), are eligible following disease progression.

[4] The patient has metastatic disease or locally advanced disease that is measurable, or nonmeasurable but evaluable, by radiological imaging per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009 [Attachment 8]). Baseline tumor assessment should be performed using a high resolution computed tomography (CT) scan using intravenous and oral contrast unless clinically contraindicated. Magnetic resonance imaging (MRI) is acceptable if a CT cannot be performed.

[5] The patient has an ECOG performance status of 0 or 1 (see Attachment 6).

[6] The patient has adequate organ function, including:

a. Total bilirubin ≤1.5 × the upper limit of institutional normal (ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN. If the liver has tumor involvement, AST and ALT <5 × ULN are acceptable.

b. Serum creatinine ≤1.5 × ULN or calculated creatinine clearance (per the Cockcroft-Gault formula or equivalent and/or 24-hour urine collection) ≥50 mL/min (Attachment 7).

c. Urinary protein is <2+ on dipstick or routine urinalysis.

If urine dipstick or routine urinalysis indicates proteinuria ≥2+, then a 24-hour urine collection must be performed and must demonstrate urine protein <2 g to allow the patient to participate in the study.

d. Absolute neutrophil count ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, and hemoglobin ≥9 g/dL (5.58 mmol/L). Packed red blood cell transfusions are not allowed within 1 week prior to baseline hematology profile.

e. International normalized ratio (INR) ≤1.5 × ULN and partial thromboplastin time ≤5 seconds above ULN, unless the patient is receiving anticoagulation therapy. Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to randomization.

[7] The patient is at least 18 years old (or of an acceptable age according to local regulations, whichever is older).

[8] The patient has provided written informed consent prior to any study-specific procedures and is amenable to compliance with protocol schedules and testing.

[9] The patient has an estimated life expectancy of ≥12 weeks in the judgment of the investigator.

[10] The patient has resolution to Grade ≤1 by Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (NCI 2009), of all clinically significant toxic effects of previous anticancer therapy. Patients with nonserious and nonlife-threatening toxicities, such as alopecia, altered taste, or nail changes, can be considered. Stable Grade 2 neuropathy is permitted.

[11] The patient, if male, is sterile (including vasectomy confirmed by post-vasectomy semen analysis) or agrees to use a reliable method of birth control and to not donate sperm during the study and for at least 12 weeks following the last dose of study treatment.

[12] The patient, if female, is surgically sterile, is postmenopausal, or agrees to use a highly effective method of birth control during the study and for 12 weeks following the last dose of study treatment.

A "highly effective method of birth control" is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly.

[13] The patient, if female and of child-bearing potential, must have a negative serum or urine pregnancy test within 7 days prior to randomization.

5.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[14] The patient has cancer with histology other than adenocarcinoma.

[15] The patient is receiving chronic therapy with any of the following within 7 days prior to randomization:

a. nonsteroidal anti-inflammatory agents (NSAIDs; such as indomethacin, ibuprofen, naproxen, or similar agents)

b. other anti-platelet agents (such as clopidogrel, ticlopidine, dipyridamole, or anagrelide)

Aspirin use at doses up to 325 mg/day is permitted.

[16] The patient received radiotherapy within 14 days prior to randomization. Palliative radiotherapy during the study, if clinically indicated, can be considered after consultation with the Lilly clinical research physician (CRP). Any lesion requiring palliative radiotherapy or which has been previously irradiated cannot be considered for response assessment.

[17] The patient received >1 line of prior therapy for the treatment of locally advanced and unresectable or metastatic gastric or GEJ (Siewert Types I-III) adenocarcinoma.

[18] The patient received previous systemic chemotherapy with a cumulative dose of >900 mg/m^2 of epirubicin or >400 mg/m^2 of doxorubicin.

[19] The patient received previous treatment with agents targeting the VEGF/VEGF Receptor 2 signaling pathway, including previous exposure to ramucirumab.

[20] The patient has documented brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression. Screening of asymptomatic patients is not required.

[21] The patient has a significant bleeding disorder or vasculitis or had a Grade ≥3 bleeding episode within 12 weeks prior to randomization.

[22] The patient experienced any arterial thromboembolic event (ATE), including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to randomization.

[23] The patient has symptomatic congestive heart failure (CHF; New York Heart Association II-IV) or symptomatic or poorly controlled cardiac arrhythmia.

[24] The patient has uncontrolled hypertension, as defined in CTCAE Version 4.0, prior to initiating study treatment, despite antihypertensive intervention.

CTCAE Version 4.0 defines uncontrolled hypertension as Grade >2 hypertension; clinically, the patient continues to experience elevated blood pressure (systolic >160 mmHg and/or diastolic >100 mmHg) despite medications).

[25] The patient underwent major surgery within 28 days prior to randomization or central venous access device placement within 7 days prior to randomization.

[26] The patient plans to undergo elective major surgery during the course of the trial.

[27] The patient has a history of gastrointestinal (GI) perforation or fistula within 6 months prior to randomization.

[28] The patient has a history of inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤12 months prior to randomization.

[29] The patient has an acute or subacute bowel obstruction or history of chronic diarrhea that is considered clinically significant in the opinion of the investigator.

[30] The patient has either of the following:

a. cirrhosis at a level of Child-Pugh B (or worse)

b. cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

[31] The patient has known allergy or hypersensitivity to any components of study treatment.

[32] The patient is currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or is concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Patients participating in surveys or observational studies are eligible to participate in this study.

[33] The patient received any previous investigational therapy within 4 half-lives of the investigational agent prior to randomization.

[34] The patient has a serious illness or medical condition including, but not limited to, the following:

a. known human immunodeficiency virus infection or acquired immunodeficiency syndrome-related illness

b. active or uncontrolled clinically serious infection

[35] The patient is pregnant or breastfeeding.

[36] The patient has a concurrent active malignancy other than the following:

a. adequately treated nonmelanomatous skin cancer

b. curatively treated in situ carcinoma of the cervix or other noninvasive carcinoma or in situ neoplasm

A patient with a history of prior malignancy is eligible if he or she has been disease free for ≥3 years prior to randomization.

[37] The patient has a serious nonhealing: (a) wound, (b) peptic ulcer, or (c) bone fracture, within 28 days prior to randomization.

[38] The patient experienced any Grade 3 or 4 venous thromboembolic event (VTE) that is considered by the investigator to be life-threatening or that is symptomatic and not adequately treated by anticoagulation therapy, within 6 months prior to randomization.

[39] The patient has any condition (for example, psychological, geographical, or medical) that does not permit compliance with the study and follow-up procedures or suggests that the patient is, in the investigator's opinion, not an appropriate candidate for the study.

5.2.1. Re-Screening

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened, only after discussion with and permission from the Lilly CRP or designee.

Repeating laboratory tests during the screening period does not constitute re-screening. Screening laboratory tests may not be repeated more than twice in order to meet eligibility during the screening period.

6. Treatment

6.1. Treatments Administered

Treatment for the first cycle should begin only if all inclusion and exclusion criteria are met and patient has been randomized to an arm of treatment via interactive web-response system (IWRS). For subsequent cycles, dose delay/modification is permitted. Missed doses will not be replaced.

Table JVCZ.1 shows the treatment regimens. The first dose of study treatment should be administered within 7 days after randomization.

Administer ramucirumab prior to paclitaxel.

Table JVCZ.1. Treatment Regimens/Dosing Schedule

		Dose and Schedule (q 28 Days)		
Arm	**N**	**Ramucirumab D1 and D15**	**Paclitaxel D1, D8, and D15**	**Route of Administration**
1	120	8 mg/kg	80 mg/m^2	Intravenous
2	120	12 mg/kg	80 mg/m^2	Intravenous

Abbreviations: D = day; N = number of randomized patients; q = every.

If, at any time during the study, Lilly determines that the safety profile of ramucirumab 12 mg/kg is unacceptable, enrollment in Arms 1 and 2 will be stopped, and 30 additional patients will be enrolled in a new treatment arm (Arm 3). Patients enrolled in Arm 3 will receive ramucirumab 10 mg/kg on Days 1 and 15 in combination with paclitaxel 80 mg/m^2 on Days 1, 8, and 15, every 28 days. For ongoing patients receiving ramucirumab 12 mg/kg, dose reduction to ramucirumab 10 mg/kg is recommended; however, if the patient is receiving ramucirumab without unacceptable toxicity, the patient may continue to receive ramucirumab 12 mg/kg at the discretion of the investigator.

If a patient cannot be treated with 1 component of the study therapy (ramucirumab or paclitaxel) for more than 28 days from the last administered dose, that component will be permanently discontinued. The other component should be continued, with the patient remaining on study, if clinically indicated.

6.1.1. Selection and Timing of Doses

A cycle is defined as an interval of 28 days. Initiation of a new treatment cycle will be defined by administration of paclitaxel. If paclitaxel cannot be administered on the planned Day 1 of the next cycle, ramucirumab will be administered within the current cycle. Once paclitaxel can be administered, the new treatment cycle will start, and ramucirumab and paclitaxel administration should be synchronized. Refer to Attachment 5 for example dosing scenarios.

A delay of a dose due to holiday, weekend, bad weather, or other unforeseen circumstance will be permitted for up to 3 days and will not be counted as a protocol deviation.

The patient's actual dose of ramucirumab will be determined by measuring the patient's weight at the beginning of each cycle. If the patient's weight fluctuates by more than ±10% from the

weight used to calculate the prior dose, the ramucirumab dose must be recalculated. Recalculation of the ramucirumab dose for weight fluctuations of <10% is permitted but not required.

The patient's first dose of paclitaxel is dependent upon the patient's baseline body surface area (BSA). Subsequent doses of paclitaxel must be recalculated if the patient's BSA changes by ≥10% from his or her baseline BSA.

For patients undergoing repeated palliative drainage procedures to remove pleural or peritoneal fluid, dry weight will be defined as weight obtained after the drainage procedure and before fluid reaccumulation. In such circumstances, dry weight will be used for dose calculation, if obtained ≤30 days prior to dose. If no recent dry weight is available, actual weight will be used.

A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

6.1.1.1. Premedication

6.1.1.1.1. Premedication Prior to Administration of Ramucirumab

Prior to each infusion of ramucirumab, premedicate all patients with an intravenous histamine H1 antagonist, such as diphenhydramine hydrochloride.

Additional premedication may be provided at investigator discretion.

See Table JVCZ.6 for ramucirumab dose modifications and additional premedication requirements for patients who have experienced a prior ramucirumab infusion-related reaction (IRR).

6.1.1.1.2. Premedication Prior to Administration of Paclitaxel

Premedication is required prior to infusion of paclitaxel according to the manufacturer's instructions and local standards. Premedication will consist of:

- dexamethasone 8 to 20 mg (or equivalent) administered:
  - orally 12 hours and 6 hours prior to paclitaxel, or
  - intravenously 30 to 60 minutes prior to paclitaxel
- an antihistamine (H1 antagonist) such as diphenhydramine hydrochloride (or equivalent) 50 mg administered intravenously
- cimetidine (H2 antagonist) (or equivalent) 300 mg administered intravenously

An antiemetic, such as ondansetron 8 mg administered orally or intravenously (or equivalent) 30 to 120 minutes before paclitaxel, is recommended.

6.1.1.2. Administration of Ramucirumab

Prior to each infusion of ramucirumab, the patient must meet the criteria shown in Table JVCZ.2.

Table JVCZ.2. Criteria to Be Met Prior to Each Ramucirumab Administration

Urine protein	• <2+ on dipstick or routine urinalysis for C1D1; ≤2+ on dipstick or routine urinalysis for subsequent infusions[a] -or- • <2 g on 24-hour urine collection
Hypertension	• Hypertension is controlled
Wound healing	• Any wound is fully healed
Ramucirumab-related toxicities and AEs (other than AESIs [see Section 6.6.1.2])	• CTCAE (Version 4.0) Grade <2 or the patient's baseline level, except for clinically insignificant AEs (such as alopecia), as determined by the investigator.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; C1D1 = Cycle 1 Day 1; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009).

[a] If urine protein =2+ on dipstick or routine urinalysis, refer to Table JVCZ.6.

If the first dose of ramucirumab cannot be administered within 7 days after the randomization date, ramucirumab must be delayed until laboratory tests are repeated (see *Laboratory Assessments* in Attachment 1).

Ramucirumab infusions should be delivered in approximately 60 minutes. The infusion rate should not exceed 25 mg/min. Infusions >60 minutes are permitted in the following situations:

1. if needed in order to maintain an infusion rate ≤25 mg/min, or
2. if the patient previously experienced a ramucirumab IRR. See Section 8.2.1.1.1 for dose modifications and premedication requirements.

6.1.1.3. Administration of Paclitaxel

On Day 1 of each cycle, the patient must meet the criteria shown in Table JVCZ.3 prior to administration of paclitaxel. On Day 8 and Day 15, the patient must meet the criteria shown in Table JVCZ.4.

Paclitaxel infusions should be delivered in approximately 60 minutes. Refer to the manufacturer's instructions for complete prescribing information and follow institutional procedures for administration of paclitaxel.

Table JVCZ.3. Criteria to Be Met Prior to Paclitaxel Administration On Day 1 of Each Cycle

Laboratory Test	Required Value
Neutrophils	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥8.0 g/dL
Serum creatinine or CrCl	≤1.5 × ULN or CrCl ≥50 mL/min
Bilirubin	≤1.5 × ULN
AST/ALT	
• if the patient has liver metastases	≤5 × ULN
• if the patient does not have liver metastases	≤3 × ULN
Paclitaxel-related toxicities/AEs (except for clinically insignificant events, as determined by the investigator)	CTCAE Grade <2 or the patient's baseline level

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; CTCAE = Common Toxicity Criteria for Adverse Events; ULN = upper limit of normal.

Table JVCZ.4. Criteria to Be Met Prior to Paclitaxel Administration On Day 8 and Day 15 of Each Cycle

Laboratory Test	Required Value
Neutrophils	≥1.0 × 10^9/L
Platelets	≥75 × 10^9/L
Hemoglobin	≥8.0 g/dL
Bilirubin	≤1.5 × ULN
AST/ALT	
• if the patient has liver metastases	≤5 × ULN
• if the patient does not have liver metastases	≤3 × ULN
Paclitaxel-related toxicities/AEs (except for clinically insignificant events, as determined by the investigator)	CTCAE Grade <2 or the patient's baseline level

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Toxicity Criteria for Adverse Events; ULN = upper limit of normal.

6.1.2. Investigator Responsibilities

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of ramucirumab and paclitaxel dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study treatment so that the situation can be assessed.

6.2. Treatment Assignment

Patients who meet all criteria for enrollment will be randomly assigned to Arm 1 or Arm 2.

The study will randomize (1:1) approximately 240 patients to the 2 treatment arms. Randomization will be stratified by ECOG performance status (0 versus 1).

Assignment to treatment arms will be determined by a computer-generated random sequence using an IWRS.

If, at any time during the study, Lilly determines that the safety profile of ramucirumab 12 mg/kg is unacceptable, 30 additional patients will be enrolled to a new treatment arm (Arm 3). For additional details, see Section 6.1.

Patients in all arms will be treated until disease progression, toxicity requiring cessation of treatment, withdrawal of consent, or other withdrawal criteria are met.

6.3. Blinding

This is an open-label study.

6.4. Packaging and Labeling

Ramucirumab will be provided by Lilly and will be labeled according to the country's regulatory requirements. In the United States, paclitaxel will be provided by the study sites. Outside of the United States, paclitaxel will be provided by Lilly and will be labeled according to the country's regulatory requirements.

6.5. Preparation/Handling/Storage

Refer to the IB for detailed information about preparation, handling, and storage of ramucirumab. Additional information is provided in the study pharmacy manual.

Refer to the manufacturer's instructions for instructions on preparation, handling, and storage of paclitaxel. Additional information for dosing is provided in the study pharmacy manual.

6.6. Dose Modification

6.6.1. Ramucirumab Dose Modifications

This section provides instructions for ramucirumab dose modifications applicable to all treatment arms. The ramucirumab dose may need to be delayed and/or reduced if the patient experiences an adverse event, including AESIs and non-AESIs.

Table JVCZ.5 presents the specific ramucirumab dose reductions applicable to each treatment arm.

Table JVCZ.5. Ramucirumab Dose Reductions[a]

Dose	Arm 1	Arm 2
Starting dose	8 mg/kg on D1, D15	12 mg/kg on D1, D15
First dose reduction	6 mg/kg on D1, D15	10 mg/kg on D1, D15
Second dose reduction	5 mg/kg on D1, D15	8 mg/kg on D1, D15

Abbreviation: D = day.

[a] Ramucirumab dose reductions are allowed between cycles and within a given cycle.

If enrollment in Arm 3 is initiated (see Section 4.1), the following ramucirumab dose reductions will apply: (1) first dose reduction, 8 mg/kg; and (2) second dose reduction, 6 mg/kg.

Any patient who requires a ramucirumab dose reduction will continue to receive a reduced dose until discontinuation from ramucirumab or discontinuation from the study.

Any patient who has had 2 ramucirumab dose reductions and who experiences an event that would cause a third dose reduction must be discontinued from ramucirumab.

6.6.1.1. Ramucirumab Dose Modifications for AESIs

Table JVCZ.6 presents the criteria for ramucirumab dose modifications applicable if the patient experiences an AESI. A list of the AESIs for ramucirumab is provided below:

Infusion-related reactions (IRRs)
Hypertension
Proteinuria
Arterial thromboembolic events (ATEs)
Venous thromboembolic events (VTEs)
Bleeding/hemorrhage
Gastrointestinal perforation
Congestive heart failure
Wound healing complications
Fistula
Liver failure/liver injury
Reversible posterior leukoencephalopathy syndrome (RPLS)

Table JVCZ.6. Dose-Modifications for Ramucirumab Adverse Events of Special Interest

Adverse Event of Special Interest		Dose Modification
1.	**Infusion-related reaction** (Section 8.2.1.1.1)	
1.a.	• Infusion-related reaction - Grade 1 or 2	Reduce the infusion rate by 50% for the duration of the infusion and for all future infusions. Prior to all future infusions of ramucirumab, premedicate with: • an intravenous histamine H1 antagonist, such as diphenhydramine hydrochloride, • dexamethasone or equivalent, and • acetaminophen
1.b.	• Infusion-related reaction - Grade 3 or 4	Discontinue ramucirumab.
2.	**Hypertension** (Section 8.2.1.1.2)	

Adverse Event of Special Interest		Dose Modification
2.a.	• Hypertension (non-life-threatening and associated with symptoms) - Grade 2 or 3	Delay ramucirumab until the hypertension is controlled with medication and is resolved to Grade <2. • If controlled with medication and resolved to Grade <2 within **14 days**, then resume ramucirumab at current dose. • If controlled with medication and resolved to Grade <2 within 28 days, then resume ramucirumab at a reduced dose as shown in Table JVCZ.5. • If **not** controlled with medication and **not** resolved to Grade <2 within **28 days**, then discontinue ramucirumab. • Investigators have the discretion to consider the clinical circumstances of individual patients, especially involving borderline hypertension, and administer unchanged dose of ramucirumab for blood pressure up to systolic 160 mm Hg and diastolic 100 mm Hg, if clinically appropriate.
2.b.	• Uncontrolled hypertension, hypertensive crisis, or hypertensive encephalopathy - Grade 4	Discontinue ramucirumab.
3.	**Proteinuria** (Section 8.2.1.1.3)	
3.a.	• Proteinuria =2+ (dipstick or routine urinalysis)[a]	• Administer ramucirumab at the patient's current dose if clinically indicated. • Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose. o If urine protein is <2 g/24 h, administer ramucirumab at the patient's current dose. o If urine protein is ≥2 g/24 h, modify the ramucirumab dose based on 24-hour collection. See *Proteinuria ≥2 g/24 h (24-hour urine collection)*, Line 3.c in this table.
3.b.	• Proteinuria >2+ (dipstick or routine urinalysis)[a]	• Delay ramucirumab dose for up to 28 days. • Obtain 24-hour urine protein results within 3 days prior to the next ramucirumab dose. o If urine protein is <2 g/24 h, no further dose delay or dose reduction is required. o If urine protein is ≥2 g/24 h, modify the ramucirumab dose based on 24-hour collection. See *Proteinuria ≥2 g/24 h (24-hour urine collection)*, Line 3.c in this table.
3.c.	• Proteinuria ≥2 g/24 h (24-hour urine collection)[a]	**First or second occurrence**: delay ramucirumab until urine protein returns to <2 g/24 h. Reduce ramucirumab dose, as shown in Table JVCZ.5. If urine protein remains ≥2 g/24 h after holding ramucirumab for 28 days, discontinue ramucirumab. **Third occurrence**: discontinue ramucirumab.

Adverse Event of Special Interest		Dose Modification
3.d.	• Proteinuria >3 g/24 h **or** in the setting of nephrotic syndrome[a]	Discontinue ramucirumab.
4.	Arterial thromboembolic events, venous thromboembolic events (Section 8.2.1.1.4) - Grade 3 or 4	Discontinue ramucirumab.
5.	Bleeding/hemorrhage (Section 8.2.1.1.5) - Grade 3 or 4	Discontinue ramucirumab.
6.	Gastrointestinal perforation (Section 8.2.1.1.6)	Discontinue ramucirumab.
7.	Reversible posterior leukoencephalopathy syndrome (Section 8.2.1.1.7)	Discontinue ramucirumab.
8.	Congestive heart failure (Section 8.2.1.1.8) – Grade 3 or 4	Discontinue ramucirumab.
9.	Fistula formation (Section 8.2.1.1.9)	Discontinue ramucirumab.
10.	Impaired wound healing (Section 8.2.1.1.10)	
10.a.	• Prior to planned surgery	• Withhold ramucirumab.
10.b	• After surgery	• Resume ramucirumab based on clinical judgment (maximum delay is 28 days after the patient's previous dose).
10.c.	• Wound-healing complications developed during study treatment	• Delay ramucirumab dosing (for up to 28 days) until the wound is fully healed.
11.	Liver injury/liver failure (Section 8.2.1.1.11)	
11.a.	• Hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis	Discontinue ramucirumab.

a Perform dipstick or routine urinalysis within 3 days prior to each infusion of ramucirumab (see Table JVCZ.2). If 24-hour urine collection is also performed, the results of 24-hour urine collection should be used for clinical decision-making.

Refer to Section 8.2.1.1 for detailed information about AESIs for ramucirumab.

6.6.1.2. Ramucirumab Dose Modifications for Non-AESIs

The ramucirumab dose may be modified if the patient experiences a Grade 3 clinical AE that meets all of the following conditions:

- the AE is reversible and non-life-threatening
- the AE is not an AESI
- the AE is considered to be at least possibly related to ramucirumab
- the AE resolves to Grade ≤1 or to the patient's pretreatment baseline level within 28 days

If the patient experiences Grade 4 fever or a Grade 4 laboratory abnormality, ramucirumab may be continued at the discretion of the investigator if the fever or laboratory abnormality resolves to Grade ≤1 or to the patient's pretreatment baseline level within 28 days.

If a second instance of Grade 4 fever or Grade 4 laboratory abnormality occurs, resume ramucirumab at a lower dose as shown in Table JVCZ.5.

Patients who enter the study with symptoms or laboratory values equivalent to Grade 1 or 2 AEs should not have dose reductions related to the persistence or mild worsening of those symptoms or laboratory values; dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the investigator. Asymptomatic laboratory abnormalities should not result in dose delays, modifications, or discontinuation of ramucirumab unless determined by the investigator to be clinically significant or life-threatening.

6.6.2. Paclitaxel Dose Modifications

This section provides instructions for paclitaxel dose modifications applicable if the patient experiences AEs or laboratory toxicities.

On Days 8 and 15 of each cycle, the patient must meet the criteria shown in Table JVCZ.4. If the patient does not meet these criteria, omit the paclitaxel dose. Refer to Attachment 5 for example dosing scenarios.

If the patient experiences any of the following CTCAE toxicities, reduce the paclitaxel dose by 10 mg/m^2 beginning at the next cycle:

- Grade 4 hematological toxicity
- Grade 3 paclitaxel-related nonhematological toxicity that is clinically significant (as determined by the investigator)

Discontinue paclitaxel if the patient experiences Grade 4 nonhematological toxicity that is related to paclitaxel.

No reductions of the paclitaxel dose are allowed within a given cycle. Any patient who requires a paclitaxel dose reduction will continue to receive a reduced dose.

Any patient who has had 2 paclitaxel dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from paclitaxel.

6.7. Treatment Compliance

The study medication will be administered only at the investigational sites by the authorized study personnel. As a result, treatment compliance is ensured.

6.8. Concomitant Therapy

A list of restricted and excluded concomitant therapies is provided in Attachment 9. All premedication, supportive care, and concomitant medication must be reported on the CRF at each visit.

The use of analgesic agents during the conduct of the study is permitted at the discretion of the investigator. The chronic use of NSAIDs with a high risk of bleeding (for example, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged except at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the patient. Chronic use of aspirin up to 325 mg/day is permitted.

Chronic use of analgesic agents with no or low bleeding risk (for example, paracetamol/acetaminophen, metamizole, dipyrone, or propyphenazone) is acceptable.

6.9. Treatment After Study Completion (Continued Access Period)

Patients receiving study treatment and experiencing ongoing clinical benefit and no undue risks may continue to receive study treatment in the continued access period until one of the criteria for discontinuation is met (Section 7.1). Crossover from 1 treatment arm to another will not be permitted. Lilly will notify investigators when the continued access period begins. The continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs.

For patients who are in short-term follow-up when the continued access period begins, follow-up will end when the short-term follow-up visit is completed.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

Procedures will be performed as shown in the *Time and Events Table for the Continued Access Period* provided in Attachment 1. During the continued access period, all AEs, SAEs, and ramucirumab exposure data will be reported on the CRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 8.2.1.2). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

7. Discontinuation Criteria

The reason for discontinuation from ramucirumab, paclitaxel, or study participation and the date of discontinuation will be collected for all randomized patients. All randomized patients who discontinue, regardless of whether or not they received ramucirumab and/or paclitaxel, will have procedures performed as shown in the *Time and Events Table* (Attachment 1).

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

7.1. Discontinuation From Study Treatment

Table JVCZ.7 presents the criteria for discontinuation of the patient from ramucirumab and/or paclitaxel. Refer to Section 6.6 for information about discontinuation from study treatment due to AEs.

Table JVCZ.7. Criteria for Discontinuation from Study Treatment With Ramucirumab and/or Paclitaxel

Criterion	Discontinue Ramucirumab	Discontinue Paclitaxel
1. The patient enrolls in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.	X	X
2. The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication; discontinuation from study treatment occurs prior to introduction of the new agent.	X	X
3. The patient experiences disease progression (assessed radiologically or clinically).	X	X
4. The patient is significantly noncompliant with study procedures and/or treatment.	X	X
5. The investigator decides the patient should be discontinued from:		
a. ramucirumab	X	
b. paclitaxel		X
6. The patient requests to be withdrawn from:		
a. ramucirumab	X	
b. paclitaxel		X
7. The patient experiences any Grade 4 AE, other than fever or laboratory abnormality, that is considered to be at least possibly related to ramucirumab.	X	
8. The patient experiences any life-threatening AE or other unacceptable toxicity that, in the opinion of the investigator:		
a. is related to ramucirumab	X	
b. is related to paclitaxel		X
c. cannot be attributed to ramucirumab or paclitaxel	X	X
9. The patient has had 2 ramucirumab dose reductions and experiences an adverse event that would require a third ramucirumab dose reduction.	X	
10. The patient has had 2 paclitaxel dose reductions and experiences an adverse event that would require a third paclitaxel dose reduction.		X

Abbreviation: AE = adverse event.

If the patient is discontinued from one study drug (ramucirumab or paclitaxel) because of toxicity, the patient may continue to receive the other study drug until progressive disease (PD) or until another criterion for discontinuation is met.

After discontinuation of all study treatment, the patient will be treated as clinically indicated by the investigator or referring physician. All patients will be followed until resolution or stabilization of any SAE or study-related toxicity.

7.1.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, Lilly must be notified.

If Lilly identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Lilly CRP and the investigator to determine whether the patient may continue in the study, with or without ramucirumab. Inadvertently enrolled patients may be maintained in the study and on ramucirumab when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without ramucirumab if the Lilly CRP does not agree with the investigator's determination it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without ramucirumab.

7.2. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- the investigator decides that the patient should be discontinued from the study
- the patient requests that the patient be withdrawn from the study
- the patient becomes pregnant during the study. See Section 8.2.1 regarding regulatory reporting requirements on fetal outcome and breast-feeding.
- Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

7.2.1. Patients Who Are Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow.

Site personnel, or an independent third party, will attempt to collect the vital status (that is, alive or dead) for all randomized patients who are lost to follow-up, including randomized patients who do not receive any dose of ramucirumab or paclitaxel, within legal and ethical boundaries. Site personnel, or an independent third party, may search public sources for vital status information. If the patient's vital status is determined, the vital status will be documented and the patient will not be considered lost to follow-up. Lilly will notify site personnel or the independent third party when to stop efforts to collect vital status.

Lilly personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Physical examinations and radiological assessments performed as part of routine clinical care may be used as baseline assessments if performed within 21 days prior to randomization.

Patients may be enrolled on study with measurable or nonmeasurable but evaluable disease based on RECIST v.1.1 (Attachment 8). If feasible, the primary gastric tumor should not be used as a target lesion for RECIST purposes.

8.1. Efficacy

Because radiographic imaging scans may be needed for future regulatory purposes or an independent review of all or a representative sample of scans may be considered following the completion of the study, copies of all scans will be collected throughout the study and stored centrally by a coordinating vendor designated by Lilly.

8.1.1. Efficacy Assessments at Baseline and During Study Treatment

Study procedures, assessments, and their timing are described in the sections below and shown in the *Time and Events Table* (Attachment 1).

Within 21 days prior to randomization, baseline tumor measurements will be performed on each patient. Computed tomography scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, MRI is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast are required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST v.1.1.

During study treatment, perform tumor assessment and imaging every 8 weeks (±7 days) from the date of the first dose of study treatment until the patient has objective PD or dies, whichever occurs first.

Except when deemed not feasible in the opinion of the investigator because of the patient's clinical status, imaging studies and tumor assessments will be performed as scheduled, even if therapy is delayed. The method of tumor assessment used at baseline must be used consistently throughout the study. Radiological scan of the thorax, abdomen, and pelvis is required.

8.1.2. Efficacy Assessments During Postdiscontinuation Follow-Up

Postdiscontinuation follow-up will be conducted as described in the *Time and Events Table* (Attachment 1).

For patients who discontinue ramucirumab without objectively measured PD, continue to perform tumor assessment and imaging as follows:

- every 8 weeks (±7 days) until the patient has objective PD or dies, or until study completion, whichever occurs first

8.1.3. Efficacy Measures

Progression-free survival (PFS) is measured from the date of randomization to the date of radiographic documentation of progression (as defined by RECIST v1.1) or the date of death due to any cause, whichever is earlier. The censoring is taken in the following order:

- if a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the enrollment date, regardless of whether or not radiographically determined disease progression or death has been observed for the patient. Otherwise,
- if a patient is not known to have died or have radiographically documented progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at date of the last complete radiographically documented progression-free disease assessment.

Best response will be derived to encompass all tumor assessments from baseline until the earliest assessment of radiographically documented progression or start of new anticancer therapy. Any responses observed after radiographically documented progression or the start of new anticancer therapy are excluded from the determination of best respo nse.

The objective response rate (ORR) is the proportion of randomized patients achieving a best overall response of complete response (CR) or partial response (PR).

The disease control rate (DCR) is the proportion of randomized patients achieving a best overall response of CR, PR, or stable disease (SD).

Overall survival (OS) is the time from the date of randomization to the date of death from any cause. If the patient was alive at the data inclusion cutoff date for the analysis (or was lost to follow-up), OS will be censored on the last date the patient was known to be alive.

8.1.4. Appropriateness of Measurements

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology trials.

8.2. Safety

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue before completing the study. The patient should be followed until the

event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the *Time and Events Table* (Attachment 1).

Laboratory assessments performed at baseline may also be used for treatment decisions on Day 1 of Cycle 1 if both of the following conditions are met:

- The baseline assessments were performed within 7 days before Day 1 of Cycle 1.
- The results are deemed still clinically valid by the treating investigator.

Table JVCZ.8 presents a summary of AE and SAE reporting guidelines. Table JVCZ.8 also shows which database or system is used to store AE and SAE data.

Table JVCZ.8. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	X	
	All AEs	X	
	SAEs related to protocol procedures	X	X
Study treatment period	All AEs	X	
	All SAEs	X	X
Short-term postdiscontinuation follow-up	All AEs	X	
	All SAEs	X	X
Long-term postdiscontinuation follow-up	All SAEs related to study treatment or protocol procedures	X	X
Continued access period	All AEs	X	
	All SAEs	X	X
Continued access follow-up	All AEs	X	
	All SAEs	X	X
After the patient is no longer participating in the study (that is, no longer receiving study treatment and no longer in follow-up)	All SAEs related to study treatment or protocol procedures that the investigator becomes aware of		X

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

8.2.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from electrocardiograms (ECGs), laboratory tests, vital sign measurements, other procedures, and so on that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy during maternal or paternal exposures to ramucirumab that occur up to 12 weeks after the last dose of study treatment should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting conditions. All AEs related to protocol procedures are reported to Lilly or its designee.

In addition, all AEs occurring after the patient receives the first dose of ramucirumab must be reported to Lilly or its designee via CRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to study procedure or study treatment via the CRF.

The investigator will decide whether he or she interprets the observed AEs as related to study treatment or study procedure. To assess the relationship of the AE to study treatment or study procedure, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Does not know:** the investigator cannot determine the causal relationship.
- **Not related**: without question, the AE is definitely not associated with the study treatment.

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study treatment or study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

CTCAE (Version 4.0) will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching CTCAE terminology, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within Medical Dictionary for Regulatory Activities (MedDRA™).

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

8.2.1.1. Adverse Events of Special Interest for Ramucirumab

Table JVCZ.6 presents the criteria for dose modifications applicable if the patient experiences an AESI. Contact the Lilly CRP if questions arise concerning AESIs.

8.2.1.1.1. Infusion-Related Reactions

As with other monoclonal antibodies, IRRs may occur during or following ramucirumab administration. Patients should be closely monitored for signs and symptoms indicative of an IRR from the initiation of the infusion in an area where resuscitation equipment and other agents (such as epinephrine and corticosteroids) are readily available.

A 1-hour observation period following the ramucirumab infusion is mandatory for the first 2 infusions. If the patient shows no evidence of an IRR with the first 2 infusions of ramucirumab, no observation period is required for subsequent infusions. In the event an IRR occurs thereafter, the 1-hour observation should be reinstituted.

Symptoms of IRRs include rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms include bronchospasm, supraventricular tachycardia, and hypotension.

If the patient experiences a Grade 2 IRR, interrupt the infusion and treat the patient with anti-allergic medication. If symptoms resolve, resume the infusion at a reduced rate (50%).

In the event of an IRR, blood samples will be collected for both PK and immunogenicity analysis at the following time points: (i) as close as possible to the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days following the IRR.

8.2.1.1.1.1. Guidelines for Reporting IRRs

Any treatment-related IRRs are defined according to the CTCAE Version 4.0 definition (*General Disorders and Administration Site Conditions*). Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (*Immune System Disorders*). In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event.

8.2.1.1.2. Hypertension

An increased incidence of severe hypertension (CTCAE Grade 3) has been reported in patients receiving ramucirumab as compared with placebo. In most cases, hypertension was controlled using standard antihypertensive treatment. Preexisting hypertension should be controlled before starting ramucirumab treatment.

Monitoring of blood pressure is required during ramucirumab therapy. Every attempt should be made to control blood pressure to systolic <140 mm Hg and diastolic <90 mm Hg prior to starting treatment with ramucirumab. Routine clinical and laboratory monitoring is required in patients who again develop hypertension or experience a deterioration in previous hypertension.

8.2.1.1.3. Proteinuria

Proteinuria is an adverse effect for all therapies targeting the VEGF/VEGF Receptor 2 pathway, including ramucirumab. Proteinuria has been associated with ramucirumab in clinical studies. The majority of events were Grade 1 or 2. Monitoring for the development or worsening of proteinuria during ramucirumab therapy is required. Discontinue ramucirumab if the patient experiences proteinuria >3 g/24 hours or nephrotic syndrome.

8.2.1.1.4. Thromboembolic Events

8.2.1.1.4.1. Arterial Thromboembolic Events

Serious, sometimes fatal ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, have been reported in clinical trials.

8.2.1.1.4.2. Venous Thromboembolic Events

Venous thromboembolic events are associated with cancer; however, the incidence of VTEs likely varies depending on the type of cancer, stage, and intensity of imaging. Additionally, VTEs have been associated with some antiangiogenic therapy, although the incidence varies depending on the type of therapy, use of concomitant chemotherapy agents, and specific disease state. VTEs have been reported from clinical studies investigating ramucirumab, particularly in the context of metastatic disease or in regions adjacent to implanted venous access devices.

8.2.1.1.5. Bleeding/Hemorrhage

Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of severe bleeding. Severe GI hemorrhages, including fatal events, have been reported in patients with gastric cancer treated with ramucirumab in combination with paclitaxel.

Serious hemorrhagic AEs have been reported from clinical studies investigating ramucirumab. Hemorrhagic complications are associated with some malignancies (that is, variceal bleeding from portal hypertension in hepatocellular carcinoma, lower GI hemorrhage from bowel metastases in ovarian carcinoma), although the rate of these complications varies considerably. As detailed in the ramucirumab IB, the incidences of hemorrhagic events to date, significant background incidence of bleeding in some malignancies, and use of concomitant antiplatelet therapy in some of the reported cases preclude any definitive association between bleeding and ramucirumab, although ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential and are detailed in the inclusion/exclusion criteria.

8.2.1.1.6. Gastrointestinal Perforation

Patients with unresected (or recurrent) primary tumors or mesenteric or peritoneal disease who participate in this clinical study may be at increased risk for GI perforation due to the nature of the disease (metastatic gastric cancer).

An infrequent incidence of GI perforations has been associated with some antiangiogenic therapeutic agents, most specifically in the context of colorectal cancer (treated with combination regimens, including anti-VEGF antibodies and cytotoxic chemotherapy) and in advanced ovarian cancer. These events may be associated with extensive abdominal/peritoneal disease burden.

Gastrointestinal perforation has been reported from clinical studies investigating ramucirumab. The incidences of these events to date and presence of significant comorbidities and risk factors preclude any definitive association with ramucirumab, although ongoing surveillance remains essential. More information about GI perforation may be found in the IB.

8.2.1.1.7. Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome is a clinical and radiologic syndrome typically consisting of reversible cortical neurological dysfunction and brain-imaging findings of subcortical edema involving the posterior circulation, particularly the occipital lobes (Hinchey et al. 1996). The symptoms of RPLS most often include generalized seizures, headache, delirium, and cortical blindness, although these may vary significantly and occasionally include focal neurological deficits (Hinchey et al. 1996; Garg 2001; Lee et al. 2008). MRI represents the most reliable method for diagnosis (Lee et al. 2008). Clinical symptoms and MRI abnormalities usually recover within days to weeks with proper management, although permanent neurologic dysfunction has been reported (Hinchey et al. 1996; Tajima et al. 1999; Garg 2001; Lee et al. 2008).

Across the clinical program to date, 2 cases of RPLS have been reported. Both cases occurred in the recently completed double-blind, randomized, placebo-controlled Phase 3 Study I4T-MC-JVBB evaluating ramucirumab in combination with irinotecan, 5-fluorouracil, and folinic acid (FOLFIRI) versus FOLFIRI in combination with placebo for patients with metastatic colorectal cancer.

Reversible posterior leukoencephalopathy syndrome should be identified and treated promptly in order to minimize potential for permanent neurological damage. Treatment encompasses careful control of blood pressure, withdrawal of potentially causative medication, and administration of anticonvulsant agents to those experiencing seizures (Stott et al. 2005).

8.2.1.1.8. Congestive Heart Failure

An increased risk of CHF has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously treated with anthracyclines. A small number of CHF events (including fatal) were also reported in patients who had received ramucirumab after prior treatment with anthracyclines in the Phase 2 and Phase 3 studies.

Treatment with ramucirumab has the potential to enhance cardiotoxicity of agents within the anthracycline/anthracenedione class of chemotherapy medications.

Patients with risk factors should be closely monitored for signs and symptoms of CHF.

Caution should be exercised when treating patients with clinically significant cardiovascular disease, such as preexisting coronary artery disease or CHF. Ramucirumab should be discontinued in the event of any Grade 3 or 4 events consistent with CHF.

8.2.1.1.9. Fistula Formation

Because fistula formation has been associated with antiangiogenic agents, patients may be at increased risk for the development of fistula when treated with ramucirumab. Some fistulas can

be resolved with surgical procedures; however, fistulas can be fatal. The impact on the quality of life of having a fistula varies according to the location and extent of the fistula (Chen and Cleck 2009).

8.2.1.1.10. Surgery and Impaired Wound Healing

Because ramucirumab is an antiangiogenic therapy, it may have the potential to adversely affect wound healing. Ramucirumab did not impair wound healing in a study conducted in animals; however, the impact of ramucirumab on serious or nonhealing wounds has not been evaluated in humans.

8.2.1.1.11. Liver Failure and Other Significant Liver Injury

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients receiving ramucirumab. Patients with 1) cirrhosis at a level of Child-Pugh Class B (or worse) or 2) cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis should not be enrolled in clinical trials with ramucirumab. "Clinically meaningful ascites" is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

8.2.1.2. Serious Adverse Events

An SAE is any adverse event from this study that results in one of the following outcomes:

- death
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event collection begins after the patient has signed the ICF and has received study treatment. If a patient experiences an SAE after signing the ICF, but prior to receiving study treatment, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-approved method. If study site personnel contact Lilly or its designee by telephone regarding an SAE, study site personnel must also immediately provide official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to study treatment.

The investigator does not need to actively monitor patients for AEs once the trial has ended, unless provided otherwise in the protocol; however, if an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study treatment, the investigator should report the SAE to Lilly, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by Lilly in aggregate periodically during the course of the trial may be found in the IB.

8.2.1.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Development Core Safety Information in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

8.2.2. Other Safety Measures

8.2.2.1. Electrocardiograms

For each patient, a single 12-lead digital ECG will be obtained according to the *Time and Events Table* (Attachment 1) as single ECG. The patient must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs are recommended to be recorded before collecting any blood for safety or PK tests. ECGs may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still

present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant finding is identified (including but not limited to changes in QT/corrected QT interval from baseline), the investigator will determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

8.2.2.2. Echocardiogram or Multiple-Gated Acquisition Scan

An echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan will be performed according to the *Time and Events Table* (Attachment 1). Additional evaluations are not required but should be performed in the setting of cardiac symptoms, at the discretion of the investigator.

Patients will undergo baseline left ventricular ejection fraction determination by ECHO or MUGA scan. This evaluation may be repeated at any time during the study if clinically indicated.

8.2.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- adverse events, including monitoring of AESIs
- If a patient experiences elevated ALT ≥5 × ULN and elevated total bilirubin ≥2 × ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT ≥3× ULN, monitoring should be triggered at ALT ≥2 × baseline.
- Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 4.

Additional reviews of safety data will be performed during the interim analyses as described in Section 9.8.

8.3. Sample Collection and Testing

Samples collected for this study will be coded with the patient number. The samples and any data generated from them can be linked back to the patient only by investigator site personnel.

Attachment 2 lists the specific laboratory tests that will be performed for this study and whether these will be performed at a central or local laboratory.

Attachment 3 lists the schedule for collection of PK, immunogenicity, and biomarker samples.

8.3.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.3.2. Biomarkers

Collection of samples for biomarker research is also part of this study. Plasma and whole blood samples will be collected.

8.3.2.1. Whole Blood for DNA Collection

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ethical review boards (ERBs) allow, a blood sample will be collected for pharmacogenetic analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to ramucirumab. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the patient number and stored for up to a maximum of 15 years, where allowed by local regulations, after the last patient visit for the study at a facility selected by Lilly. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows Lilly to respond to regulatory requests related to ramucirumab.

Samples will be destroyed according to a process consistent with local regulation.

8.3.2.2. Plasma for Biomarkers

Plasma (from whole blood) will be used for the analyses of various biomarkers related to pathways associated with gastric cancer and the mechanism of ramucirumab, and/or angiogenesis; and for related research methods or validation of diagnostic tools or assays. Potential pharmacodynamics and/or circulating markers may include, but are not limited to, VEGF-A, VEGF-C, VEGF-D, placental growth factor, soluble VEGF Receptor 1, soluble VEGF Receptor 2, and soluble VEGF Receptor 3.

The plasma samples will be stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by Lilly or its designee. The duration allows Lilly to respond to regulatory requests related to the study treatment.

8.3.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against ramucirumab. The schedule for collection of these blood samples is provided in Attachment 3.

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies in the presence of ramucirumab. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of ramucirumab.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by Lilly to enable further analysis of immune responses to ramucirumab. The duration allows Lilly to respond to regulatory requests related to ramucirumab

8.3.4. Pharmacokinetics

Blood samples will be collected from all randomized patients to assess ramucirumab concentrations in serum. The schedule for collection of these blood samples is provided in Attachment 3.

Bioanalytical samples collected to measure ramucirumab concentration will be retained for a maximum of 1 year following last patient visit for the study.

9. Statistical Considerations and Data Analysis

9.1. Determination of Sample Size

Estimation of the sample size for this study was performed to ensure adequate statistical power for both a conventional analysis of PFS, with a log-rank test for ramucirumab doses of 12 mg/kg versus 8 mg/kg using data from Study JVCZ alone, and a network meta-analysis with RAINBOW for comparing ramucirumab dose of 12 mg/kg with placebo.

The sample size to test PFS for the comparison of ramucirumab doses of 12 mg/kg and 8 mg/kg using data from Study JVCZ alone was determined based on the following assumptions:

- $\alpha = 0.05$ (2-sided)
- statistical power = 80%
- randomization 1:1
- hazard ratio (HR)=0.667, targeting a 2-month increase in median PFS from 4 months (ramucirumab 8 mg/kg) to 6 months (ramucirumab 12 mg/kg)
- Accrual rate: 0-1m: 2 pts; 1-2m: 4 pts; 2-3m: 5 pts; >3m: 7.5 pts/m

Under these assumptions, approximately 191 PFS events from 228 patients will be needed. Assuming 5% early drop outs (such as patients withdrawing consent or lost to follow-up), 240 patients will be randomized in this study. With the assumed accrual rate, the estimated study duration is 36 months.

The sample size to test PFS for the comparison of the ramucirumab dose of 12 mg/kg in Study JVCZ with placebo in RAINBOW using meta-analysis with RAINBOW was determined based on the following assumptions:

- $\alpha = 0.05$ (2-sided)
- statistical power = 90%
- HR=0.635*0.667=0.424, where:
    - 0.635 is the observed HR (ramucirumab 8 mg/kg compared with placebo) in RAINBOW, and
    - 0.667 is the assumed HR (ramucirumab 12 mg/kg compared with 8 mg/kg) in Study JVCZ.

Denote:

- HR_1 = HR from RAINBOW (8 mg/kg compared with placebo), and $Z_1 = -\ln(HR_1)$
- HR_2= HR from this study (12 mg/kg compared with 8 mg/kg), and $Z_2 = -\ln(HR_2)$

then, the sample size can be determined based on the test statistic $Z = Z_1 + Z_2$ with variance $Var(Z) = Var(Z_1) + Var(Z_2)$. Specifically, given a true HR (new ramucirumab dose compared with placebo) ϖ, the sample size is determined by:

$$Var(Z) = \left(\frac{\ln(\omega)}{z_{\alpha/2} + z_{\beta}}\right)^2$$

Given $Var(Z_1) = 0.007$ from RAINBOW and $Var(Z_2) = 4/(\text{number of events})$, 64 PFS events are required for this study. Therefore, the sample size of 191 events, as determined by the test for ramucirumab 12 mg/kg compared with ramucirumab 8 mg/kg, is also sufficient for the meta-analysis.

This sample size is also adequate for safety and PK analysis.

9.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly.

Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to randomized treatment.

Safety analyses will be based on the safety population, defined as all enrolled patients receiving at least a partial dose of ramucirumab or paclitaxel. Patients will be grouped according to treatment received in Cycle 1. Pharmacodynamic and/or tailoring biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all confidence intervals (CIs) will be 2-sided, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol.

Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.3. Treatment Group Comparability

9.3.1. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

9.3.2. Patient Characteristics

Description of patient characteristics at baseline, such as patient demographics, baseline disease characteristics, preexisting conditions, and prior therapies , will be reported using descriptive statistics.

9.3.3. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

9.3.3.1. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, o r systemic therapy), and by drug name.

9.3.4. Treatment Compliance

The number of dose omissions, reductions, and delays, the number of cycles received, and dose intensity will be summarized for all treated patients per treatment arm.

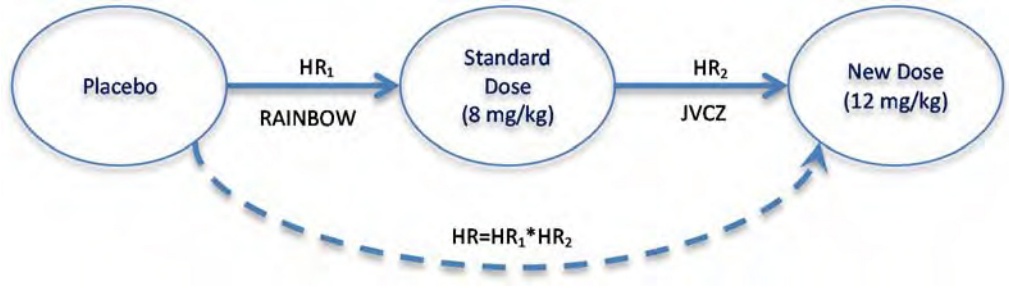
9.4. Efficacy Analysis

9.4.1. Progression-Free Survival

Two PFS analyses will be performed utilizing gatekeeping strategy to control the overall α=0.05:

- first, test ramucirumab 12 mg/kg compared with placebo, in combination with paclitaxel , and
- then, test ramucirumab 12 mg/kg compared with ramucirumab 8 mg/kg, in combination with paclitaxel.

The primary analysis (PFS Analysis 1) is the comparison of ramucirumab 12 mg/kg plus paclitaxel in this study and placebo plus paclitaxel in RAINBOW. PFS Analysis 1 will be performed using a simple network meta-analysis anchoring on the 8-mg/kg ramucirumab plus paclitaxel arm common to Study JVCZ and RAINBOW.



Denote:

- HR_1 = HR from RAINBOW (8 mg/kg compared with placebo), and $Z_1 = -\ln(HR_1)$
- HR_2= HR from this study (12 mg/kg compared with 8 mg/kg), and $Z_2 = -\ln(HR_2)$

then:

- the test statistic $Z = Z_1+Z_2$ with variance $Var(Z) = Var(Z_1) + Var(Z_2)$. The Z_i and its variance will be estimated from Cox model in each study.
- the HR of ramucirumab 12 mg/kg compared with placebo will be estimated as $HR=HR_1*HR_2$, with CI derived as exponential of the CI of $-Z(= -\ln(HR))$.

The key assumption for PFS Analysis 1 is that, as in any meta-analysis, the populations in this study and RAINBOW are similar with respect to any predictive factors, especially that patients receiving ramucirumab 8 mg/kg in the 2 studies will perform similarly.

PFS Analysis 2 is the comparison of ramucirumab 8 mg/kg (Arm 1) and ramucirumab 12 mg/kg (Arm 2) using data from Study JVCZ alone. A stratified log-rank test will be conducted to compare the 2 arms. The HR will be estimated using a stratified Cox regression model.

Survival curves and median with 95% CIs will be given using Kaplan-Meier method.

Additional sensitivity analyses taking into account clinical progression or stratification-factor data reported on the CRF or using alternative censoring rules will be specified in the statistical analysis plan. Univariate and multivariate Cox regression models will be used to explore potential prognostic and/or predictive factors.

9.4.2. Objective Response Rate and Disease Control Rate

The best overall response will be determined using the RECIST v.1.1 guidelines.

The ORR will be calculated as the number of randomized patients who achieve a best overall response of CR or PR, divided by the total number of patients randomized to the corresponding treatment arm (the ITT population). Additionally, a subgroup analysis will be performed for patients with measureable disease and for patients with nonmeasurable disease. Patients who do not have a tumor response assessment for any reason will be considered as nonresponders and are included in the denominator when calculating the response rate. The ORR with 95% CI observed in each treatment group will be summarized and compared using the Cochran-Mantel-Haenszel test adjusting for the randomization strata. The DCR will be calculated as the number of patients who achieve a best overall response of CR, PR, or SD, divided by the total number of patients randomized to the corresponding treatment group. DCR will be analyzed similarly to ORR.

9.4.3. Overall Survival

Overall survival will be analyzed similarly to PFS Analysis 1 and Analysis 2. Univariate and multivariate Cox regression model may be used to explore potential prognostic and/or predictive factors.

9.5. Safety Analyses

All safety summaries and analyses will be based on the safety population as defined in Section 9.2.

Adverse events will be summarized by MedDRA System Organ Class/Preferred Term (PT), classified from verbatim terms. The incidence and percentage of patients with at least 1 occurrence of a PT will be included, according to the most severe CTCAE Version 4.0 grade (NCI 2009). Causality (relationship to ramucirumab), action taken, and outcome will be summarized separately. Duration of AEs will be determined and included in the listings.

Exposure to study treatment will be summarized for each treatment arm with the following variables: number of infusions, number of cycles, duration of therapy, cumulative dose, dose intensity, and relative dose intensity. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle.

Laboratory results will be classified according to CTCAE Version 4.0 grade. The incidence of laboratory abnormalities will be summarized.

Hospitalizations due to AEs, transfusions, and vital signs will be summarized.

9.6. Pharmacokinetic Analyses

Serum concentrations of ramucirumab prior to infusion (minimum concentration) and at 1 hour after the end of the ramucirumab infusion (approximately maximum concentration) will be summarized using descriptive statistics. Additional analyses utilizing the population PK approach may also be conducted if deemed appropriate.

The relationship between ramucirumab exposure and selected efficacy and safety outcomes may be explored.

9.6.1. Biomarker Analyses

Biomarkers will be analyzed for associations with clinical outcomes.

9.7. Other Analysis

9.7.1. Immunogenicity Analyses

The number and percentage of patients with positive anti-ramucirumab antibodies will be summarized. Any relationship with the occurrence of an IRR and positive anti-ramucirumab antibodies may be explored.

9.8. Interim Analyses

Interim analyses of safety and PK will be conducted at the following time points:

1. after approximately a total of 80 patients complete 6 weeks of therapy, or discontinue treatment due to other reasons, whichever comes first, and
2. after approximately a total of 160 patients complete 6 weeks of therapy, or discontinue treatment due to other reasons, whichever comes first.

An assessment committee internal to Lilly will review AE profiles, AESIs, dose modifications, reasons for patient discontinuations, and other safety data at each interim analysis to determine

whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment. There will be no prespecified rules for stopping the trial due to safety concerns.

No efficacy data will be included in the interim analyses.

Unplanned interim analyses for safety may be performed during the course of the study should safety concerns arise. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

10. Regulatory and Ethical Considerations, Including the Informed Consent Process

10.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study treatment.

10.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites. The ERBs will review the protocol as required.

The study sites' ERBs should be provided with the following:

- the current IB or package labeling and updates during the course of the study
- the ICF
- relevant curricula vitae

10.2.1. Subgroup Analyses

Subgroup analysis may be performed as deemed appropriate. A prespecified list of subgroups, which are based on important characteristics, will be identified in the statistical analysis plan.

10.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- ICH GCP Guideline (E6)
- applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERBs.

Some of the obligations of Lilly will be assigned to a third-party organization.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

10.4. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

10.5. Protocol Signatures

Lilly's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

10.6. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Lilly will select an investigator to serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.7. Complaint Handling

Lilly collects product complaints on investigational products used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.8. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate

- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

10.8.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the Lilly-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10.9. Study and Site Closure

10.9.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges discontinuation of study site participation necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.9.2. Discontinuation of the Study

The study will be discontinued if Lilly judges discontinuation of the study necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

11. References

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Attachment 1. Protocol JVCZ Time and Events Table

Time and Events Table, Protocol I4T-MC-JVCZ

		Baseline (within 21 days prior to randomization)		All Treatment Cycles[a] (28-day cycles)			Postdiscontinuation Follow-Up[b,c]	
		≤21	≤7	Day 1	Day 8	Day 15	Short-Term Follow-Up Visit[d] Visit 801	Long-Term Follow-Up Visit 802-8XX
Procedures	**Prot. Ref.**							
Informed consent[e]	Sec. 8	X						
Inclusion/exclusion criteria review	Sec. 5	X						
Medical history[f]	Sec. 8.2.1.2	X						
ECG	Sec. 8.2.2.1	X					X	
Echocardiogram or MUGA scan	Sec. 8.2.2.2	X						
ECOG PS	Sec. 5, Att. 6	X		X[g]			X	
Concomitant therapy[h]	Sec. 6.8	X		X			X	
Physical exam		X		X[u]			X	
Height, weight, and BSA[i]	Sec. 6.1.1	X		X				
Vital signs[j]		X		X	X	X	X	
AE collection; CTCAE grading	Sec. 8.2	X		X	X	X	X[k]	X[l]
Laboratory Assessments[m]								
Hematology profile[n]	Sec. 8.2, Att. 2		X	X	X	X	X	
Coagulation profile[o]	Att. 2		X				X	
ALT, AST, total bilirubin	Att. 2				X	X		
Full chemistry profile[p]	Sec. 8.2, Att. 2		X	X			X	
TSH and Free T4	Att. 2		X				X	
Urinalysis[q]	Sec. 6.1.1.2, Att. 2		X	X			X	
Pregnancy test[r]	Att. 2		X				X	
Efficacy Assessments								
Survival information	Sec. 8.1.3						X[s]	X[s]
Tumor assessment and imaging[t]	Sec. 8, Att. 8	X[u]		X[v]			X[w]	X[w]

		Baseline (within 21 days prior to randomization)		All Treatment Cycles[a] (28-day cycles)			Postdiscontinuation Follow-Up[b,c]	
		≤21	≤7	Day 1	Day 8	Day 15	Short-Term Follow-Up Visit[d] Visit 801	Long-Term Follow-Up Visit 802-8XX
Procedures	**Prot. Ref.**							
Additional Analyses								
• Biomarkers • Pharmacokinetics • Immunogenicity	Sec. 8.3, Att. 3							
Treatment Administration[x]	Sec. 6.1							
Administer ramucirumab				X		X		
Administer paclitaxel				X	X	X		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Att. = attachment; BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ERB = ethical review board; ICF = informed consent form; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PD = progressive disease; Prot. Ref. = protocol reference; SAE = serious adverse event; Sec. = Section; TSH = thyroid-stimulating hormone.

a Day 1, Day 8, and Day 15 assessments are performed only if dosing is scheduled to occur on that day.

b No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

c Postdiscontinuation follow-up begins on the day after the patient and the investigator agree that the patient will no longer continue study treatment.

d The short-term follow-up visit occurs approximately 30 days (±7 days) after the day the patient and the investigator agree that the patient will discontinue from all study treatment.

e Obtain prior to any study-specific procedures. If the ICF is revised during the course of the study, re-consenting of patients may be required if deemed necessary by Lilly or the ERB.

f Including preexisting conditions, historical illnesses, and prior treatment.

g A time window of -3 days is permitted for the Cycle 1 Day 1 assessment.

h Concomitant medications will be recorded, including any taken within 30 days prior to randomization and those taken during the 30 days after the last dose of study treatment.

i Measure height at baseline only. During all treatment cycles, measure weight at the beginning of each cycle; recalculate the ramucirumab and/or paclitaxel dose if needed.

j Vital signs include temperature, pulse rate, and blood pressure. For the patient's first 2 doses of ramucirumab, measure all vital signs at the following time points: (i) within 15 minutes prior to the infusion, (ii) after completion of the infusion, and (iii) at the end of the postinfusion observation period. For all infusions of paclitaxel and all subsequent infusions of ramucirumab, measure blood pressure and pulse prior to the infusion and measure other vital signs as clinically indicated.

[k] All AEs/SAEs will be followed for up to 30 days after the patient and investigator agree that the patient will no longer continue study treatment.

[l] During long-term follow-up, only SAEs that are related to ramucirumab, paclitaxel, or protocol procedures will be collected. Follow-up should be attempted at regularly scheduled intervals (every 90 days [±7 days]) until death or for up to 1 year after the date the last patient was randomized (whichever occurs first). This follow-up might be a phone call to the patient, her/his family, or local doctor.

[m] All treatment decisions will be based on local laboratory reports.

[n] **Hematology profile:** (1) Baseline assessments can be used for treatment decisions for Cycle 1 Day 1 if the baseline assessments were performed within 7 days prior to Cycle 1 Day 1 and the results are deemed still clinically valid by the treating investigator.
(2) For subsequent infusions, perform within 3 days prior to each infusion of ramucirumab and/or paclitaxel.
(3) In the event a patient permanently discontinues paclitaxel and continues on ramucirumab monotherapy, perform within 3 days prior to Day 1 of each cycle; thereafter, a hematology profile is not required prior to infusion of ramucirumab on Day 15, unless clinically indicated.

[o] **Coagulation profile:** Baseline assessments can be used for treatment decisions for Cycle 1 Day 1 if the baseline assessments were performed within 7 days prior to Cycle 1 Day 1 and the results are deemed still clinically valid by the treating investigator. Thereafter, perform within 3 days prior to Day 1 of every odd-numbered cycle.

[p] **Chemistry profile:** Baseline assessments can be used for treatment decisions for Cycle 1 Day 1 if the baseline assessments were performed within 7 days prior to Cycle 1 Day 1 and the results are deemed still clinically valid by the treating investigator. Thereafter, perform within 3 days prior to Day 1 of each cycle.

[q] **Urinalysis:** Perform dipstick or routine urinalysis at baseline and within 3 days prior to Day 1 of each cycle. Baseline assessments can be used for treatment decisions for Cycle 1 Day 1 if the baseline assessments were performed within 7 days prior to Cycle 1 Day 1 and the results are deemed still clinically valid by the treating investigator. If baseline urine protein ≥2+ on dipstick or routine urinalysis, 24-hour urine protein results must be obtained prior to the first infusion. See Table JVCZ.6 for information about dose modifications required for proteinuria.

[r] **Pregnancy test:** Required for women of child-bearing potential. If required per local regulations and/or institutional guidelines, pregnancy testing can also be performed at other times during the study treatment period.

[s] Follow-up for the collection of survival data and subsequent anticancer treatments should be attempted at regularly scheduled intervals (every 90 days [±7 days]) until death or overall study completion, whichever is earlier. This follow-up might be a phone call to the patient, her/his family, or local doctor.

[t] Radiological scan of thorax, abdomen, and pelvis is required; MRI may be used as a complementary method for assessment of the abdomen and pelvis.

[u] Assessments previously obtained as part of routine clinical care may be used as the baseline assessment if performed within 21 days prior to randomization.

[v] Perform tumor assessment and imaging every 8 weeks (±7 days) until the patient has objective PD or dies, whichever occurs first. Perform as scheduled even if study treatment is delayed, except when tumor assessment and imaging are not feasible in the opinion of the investigator because of the patient's clinical status. Imaging is not required on Cycle 1 Day 1. The method of tumor assessment used at baseline must be used consistently throughout the study.

[w] For patients who discontinue all study treatment without objectively measured PD, continue to perform tumor assessment and imaging every 8 weeks (±7 days) until the patient has objective PD or dies or until study completion, whichever comes first.
Tumor assessments and imaging should be performed, except when tumor assessment and imaging are not feasible in the opinion of the investigator because of the patient's clinical status. After the patient has objective disease progression, tumor assessments and imaging are no longer required.

[x] The first treatment will be administered within 7 days following randomization. In the event of a medication error, sites must inform Lilly within 24 hours of becoming aware of the error.

[y] **ALT, AST, and total bilirubin:** Perform with 3 days prior to infusion of paclitaxel on Day 8 and Day 15 of each cycle.

Time and Events Table for the Continued Access Period only, Protocol I4T-MC-JVCZ

		Patients on Study Treatment			Continued Access
	Cycle	X-Y			Follow-Up[a,b]
	Visit	501-5XX			901
	Relative day within a cycle	1	8	15	
Procedure	**Protocol Reference**				
Adverse Events Collection/CTCAE Grading[c]	Sec. 8.2	X			X
Immunogenicity: Anti-ramucirumab antibodies[d]	Sec. 8.3.3, Att. 3				X
Administer ramucirumab	Sec. 6.1	X	X		
Administer paclitaxel	Sec. 6.1	X	X	X	

Abbreviations: Att. = Attachment; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; PK = pharmacokinetics; SAEs = serious adverse events; Sec. = Section.

a No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

b Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days (±7 days).

c Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

d If a patient experiences an IRR to ramucirumab, blood samples for immunogenicity and PK analysis will be taken at the following time points: (1) as soon as possible after the onset of the IRR, (2) at the resolution of the IRR, and (3) 30 days after the IRR.

Note: Efficacy assessments will be done at the investigator's discretion based on the standard of care.

Attachment 2. Protocol JVCZ Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology - local laboratory only:

Whole Blood Concentrations of the following:

Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Mean cell volume
Mean cell hemoglobin concentration
Leukocytes (WBC)
Neutrophils[b]
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Coagulation Tests - local laboratory only:

Prothrombin time (PT or INR)
Partial thromboplastin time (PTT or aPTT)

Pregnancy Test (applies only to women of child-bearing potential) - local laboratory only: Serum or urine

Thyroid Tests - central laboratory only:

TSH/Free T4 (to be collected at baseline and short-term follow-up)

Clinical Chemistry - local and central laboratories:[a]

Serum Concentrations of the following:

Sodium
Potassium
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN) or blood urea
Creatinine
Urate
Calcium
Glucose, random
Albumin

Urinalysis - local laboratory only:

Dipstick or routine urinalysis.
If urine dipstick or routine urinalysis indicates proteinuria ≥2+, a 24-hour urine collection (to assess protein) must be obtained.

Abbreviations: aPTT = activated partial prothrombin time; CRF = case report form; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; TSH = thyroid-stimulating hormone; WBC = white blood cells.

[a] Treatment decisions will be based on local laboratory results.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

Attachment 3. Protocol JVCZ Sampling Schedule for Pharmacokinetics, Immunogenicity, and Biomarkers

It is essential that the exact infusion start and stop times (actual clock readings) are recorded in the source document. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. It is essential that the PK blood samples not be withdrawn from the same site as the drug infusion.

Table ATT.3.1. Pharmacokinetic, Immunogenicity, and Biomarker Collection Timepoints

Visit	Study Day	Time	PK[a]	IK[a]	Biomarker Collection	
					Plasma	Whole Blood
Cycle 1 Day 1	Day 1	Prior to infusion	X	X	X	X[b]
Cycle 1 Day 1	Day 1	Within 1 to 1.5 hours after the end of the infusion	X			
Cycle 1 Day 15	Day 15	Within 3 days prior to infusion	X			
Cycle 2 Day 1	Day 29	Within 3 days prior to infusion	X			
Cycle 2 Day 15	Day 43	Within 3 days prior to infusion	X			
Cycle 2 Day 15	Day 43	Within 1 to 1.5 hours after the end of the infusion[e]	X			
Cycle 3 Day 1	Day 57	Within 3 days prior to infusion	X	X	X	
Cycle 3 Day 15	Day 71	Within 3 days prior to infusion	X			
Cycle 4 Day 1	Day 85	Within 3 days prior to infusion	X			
Cycle 4 Day 1	Day 85	Within 1 to 1.5 hours after the end of the infusion	X			
Short-term follow-up	Any	Anytime during the follow-up visit	X	X	X	

Abbreviations: IK = immunogenicity; IRR = infusion-related reaction; PK = pharmacokinetics.

[a] In the event of an IRR, blood samples will be collected for both PK and IK analysis at the following timepoints: (i) as soon as possible after the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days following the IRR.

[b] It is highly recommended to draw the whole blood sample prior to the first infusion of ramucirumab. However, it can be collected later during the study if necessary.

Attachment 4. Protocol JVCZ Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly clinical research physician. Additional tests, not specified below, may also be required under specific circumstances to investigate the hepatic abnormality.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; IgM = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 5. Protocol JVCZ Dosing Scenarios for Ramucirumab and Paclitaxel

Dosing Scenarios for Ramucirumab and Paclitaxel

Cycle[a]	Day	Administer Ramucirumab?	Administer Paclitaxel?
Scenario 1: Planned Dosing for Ramucirumab and Paclitaxel			
n	1	Yes	Yes
	8	No	Yes
	15	Yes	Yes
n+1	1	Yes	Yes
	8	No	Yes
	15	Yes	Yes
Scenario 2: Ramucirumab Delay on Day 1			
n	1	Delay	Yes
	8	Yes	Yes
	15	Yes	Yes
Scenario 3: Ramucirumab Delay on Days 1 and 8			
n	1	Delay	Yes
	8	Delay	Yes
	15	Yes	Yes
Scenario 4: Ramucirumab Delay on Days 1, 8, and 15			
n	1	Delay	Yes
	8	Delay	Yes
	15	Delay until Day 1 of Cycle n+1	Yes
Scenario 5: Ramucirumab Delay of up to 28 Days After the Planned Treatment Date			
n	1	Delay	Yes
	8	Delay	Yes
	15	Delay until Day 1 of Cycle n+1	Yes
Scenario 6: Ramucirumab Delay on Day 15			
n	1	Yes	Yes
	8	No	Yes
	15	Delay until Day 1 of Cycle n+1	Yes
Scenario 7: Paclitaxel Delay on Planned Day 1 (Actual Day 29)			
n	Planned Day 1 of the next cycle (Actual Day 29 of the current cycle)	Yes	Delay the start of Cycle n+1 until the patient meets the dosing criteria shown in Table JVCZ.3. Repeat blood counts and serum chemistry weekly to determine if paclitaxel can be administered.

Cycle[a]	Day	Administer Ramucirumab?	Administer Paclitaxel?
Scenario 7.a: Paclitaxel Can Be Administered on Planned Day 8 (Actual Day 1)			
n	Planned Day 1 of the next cycle (Actual Day 29 of the current cycle)	Yes	No
n+1	1	Yes	Yes
	8	No	Yes
	15	Yes	Yes
Scenario7.b: Paclitaxel Can Be Administered on Planned Day 15 (Actual Day 1)			
n	Planned Day 1 of the next cycle (Actual Day 29 of the current cycle)	Yes	No
	Planned Day 8 of the next cycle (Actual Day 36 of the current cycle)	No	No
n+1	1	Yes	Yes
	8	No	Yes
	15	Yes	Yes
Scenario 8: Paclitaxel Omitted on Day 8			
n	1	Yes	Yes
	8	No	Omit
	15	Yes	Yes
Scenario 9: Paclitaxel Omitted on Day 15			
n	1	Yes	Yes
	8	No	Yes
	15	Yes	Omit

[a] n = any cycle; n+1 = the next cycle; n-1 = the previous cycle.

Attachment 6. Protocol JVCZ ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Source: Oken et al. 1982.

Attachment 7. Protocol JVCZ Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

$$\text{CrCl} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ (\text{if female}),\ \text{or} \times \mathbf{1.0}\ (\text{if male})}{\mathbf{72} \times \mathbf{serum\ creatinine}\ (mg/dL)}\ (\text{mL/min})$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl} = \frac{(\mathbf{140 - age}^{a}) \times (\mathbf{wt}) \times \mathbf{0.85}\ (\text{if female}),\ \text{or} \times \mathbf{1.0}\ (\text{if male})}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ (\mu mol/L)}\ (\text{mL/min})$$

[a] age in years, weight (wt) in kilograms.

Reference: Cockcroft and Gault 1976.

Attachment 8. Protocol JVCZ RECIST 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

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

Special Considerations for Lesion Measurability

Bone Lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Nontarget Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the CRF in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with intravenous contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without intravenous contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will be considered measurable only when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR).

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

PET Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/ non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The best overall response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table ATT.8.1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table ATT.8.1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Nontarget 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 all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table ATT.8.2 is to be used when patients have *nonmeasurable* disease only.

Table ATT.8.2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; SD = stable disease.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. Normally, all target and nontarget sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Attachment 9. Protocol JVCZ Permitted and Prohibited Concomitant Therapy

Below is a table of medications and drug classes that either have restricted use (see the *Conditions for Use* column and referenced guidelines) or are not permissible for use while the patient is on study.

Therapy	As Needed	Chronic Use	Conditions for Use
Anticoagulants other than warfarin	yes	yes	Careful evaluation is required if patients need to be administered anticoagulation during study treatment. Note that increased risk of hemorrhage is a boxed warning in the ramucirumab package insert. Use of warfarin is prohibited. Refer to Inclusion Criterion [6] e.
Biologic response modifiers	no	no	
Chemotherapy	no	no	
Colony-stimulating factors	yes	no	Follow local guidelines.
Erythroid growth factors	yes	no	Follow local guidelines.
Experimental medicines	no	no	
Investigational agents	no	no	
NSAIDs	yes	no	Chronic use of aspirin up to 325 mg/day is permitted.
Radiotherapy	yes	no	Palliative radiotherapy during the study, if clinically indicated, can be considered after consultation with the Lilly CRP.

Abbreviations: CRP = clinical research physician; NSAIDs = nonsteroidal anti-inflammatory drugs.

Attachment 10. Protocol JVCZ Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT/PTT	activated partial prothrombin time / partial thromboplastin time
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BSA	body surface area
CHF	congestive heart failure
CI	confidence interval
collection database	A computer database where clinical trial data are entered and validated.
CR	complete response
CRF	case report form: Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.

Term	Definition
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form (ICF) directly or through their legally acceptable representatives.
ERB	ethical review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
FOLFIRI	irinotecan, 5-fluorouracil, and folinic acid
GCP	good clinical practice
GEJ	gastroesophageal junction
GI	gastrointestinal
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Term	Definition
IRR	infusion-related reaction
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NSAIDs	nonsteroidal anti-inflammatory drugs
ORR	objective response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
PTT	partial thromboplastin time
randomize	the process of assigning patients to an experimental group on a random basis
RBC	red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors

Term	Definition
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event
WBC	white blood cells

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