Protocol I4T-JE-JVCW(c)

A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

NCT02539225

Approval Date: 29-Aug-2016

1. Protocol I4T-JE-JVCW(c)

A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Confidential Information

The information contained in this protocol is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of [ramucirumab (LY3009806)], unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

Note to Regulatory Authorities: This document may contain protected personal data and/or commercially confidential information exempt from public disclosure. Eli Lilly and Company requests consultation regarding release/redaction prior to any public release. In the United States, this document is subject to Freedom of Information Act (FOIA) Exemption 4 and may not be reproduced or otherwise disseminated without the written approval of Eli Lilly and Company or its subsidiaries.

Ramucirumab (LY3009806)

This is a randomized, placebo-controlled, double-blind, Phase 2 study of patients with metastatic gastric or gastroesophageal junction adenocarcinoma. Patients will be randomized to receive ramucirumab drug product (8 mg/kg) in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin administered every 3 weeks followed by treatment with ramucirumab plus paclitaxel every 4 weeks.

Eli Lilly Japan K.K.
Protocol Electronically Signed and Approved by Lilly: 05-Jun-2015
Amendment (a) Electronically Signed and Approved by Lilly: 30-Jul-2015
Amendment (b) Electronically Signed and Approved by Lilly: 04-Nov-2015
Amendment (c) Electronically Signed and Approved by Lilly
on approval date provided below.

Approval Date: 29-Aug-2016 GMT

2. Synopsis

Clinical Protocol Synopsis: Study I4T-JE-JVCW

Name of Investigational Product: Ramucirumab (LY3009806)	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma	

Number of Planned Patients: Entered: 213 Enrolled/Randomized: 190	**Phase of Development:** 2

Length of Study: approximately 31 months
Planned first patient visit: August 2015   **Planned last patient visit*:** February 2018
* Planned data cut-off date for the primary analysis

Objectives: The primary objective of this study is to compare progression-free survival (PFS) of ramucirumab in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin as first-line treatment in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Secondary objectives of this study are to assess and compare ramucirumab in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin for the following:

- progression-free survival 2 (PFS2)
- overall survival (OS)
- objective response rate (ORR)
- disease control rate (DCR)
- pharmacokinetics (PK) of ramucirumab and anti-ramucirumab antibodies (immunogenicity)
- safety and toxicity profile

The exploratory objectives of the study are to assess the following:

- ORR of second-line therapy (ORR2)
- DCR of second-line therapy (DCR2)
- PFS of second-line therapy (PFS2-1)
- OS of second-line therapy (OS2)
- the relationship between biomarkers and clinical outcomes.

Study Design: This is a multicenter, randomized, placebo-controlled, double-blind, Phase 2 study of patients with metastatic gastric or GEJ adenocarcinoma. Patients will be randomized to receive ramucirumab (8 mg/kg) in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin (Part A) followed by open-label treatment with ramucirumab plus paclitaxel (Part B).

Patients will receive intravenous (IV) ramucirumab/placebo on Days 1 and 8, every 21 days, in combination with S-1 and oxaliplatin (Part A). Ramucirumab/placebo, S-1, and oxaliplatin will be continued until disease progression, development of unacceptable toxicity, or any other discontinuation criteria are met. After discontinuation of treatment in Part A, assessments of pre-treatment of Part B will be done and patients who meet initiation criteria for Part B will receive I.V. ramucirumab on Days 1 and 15, every 28 days, in combination with paclitaxel. The treatment schema for each arm is summarized in the figure below.
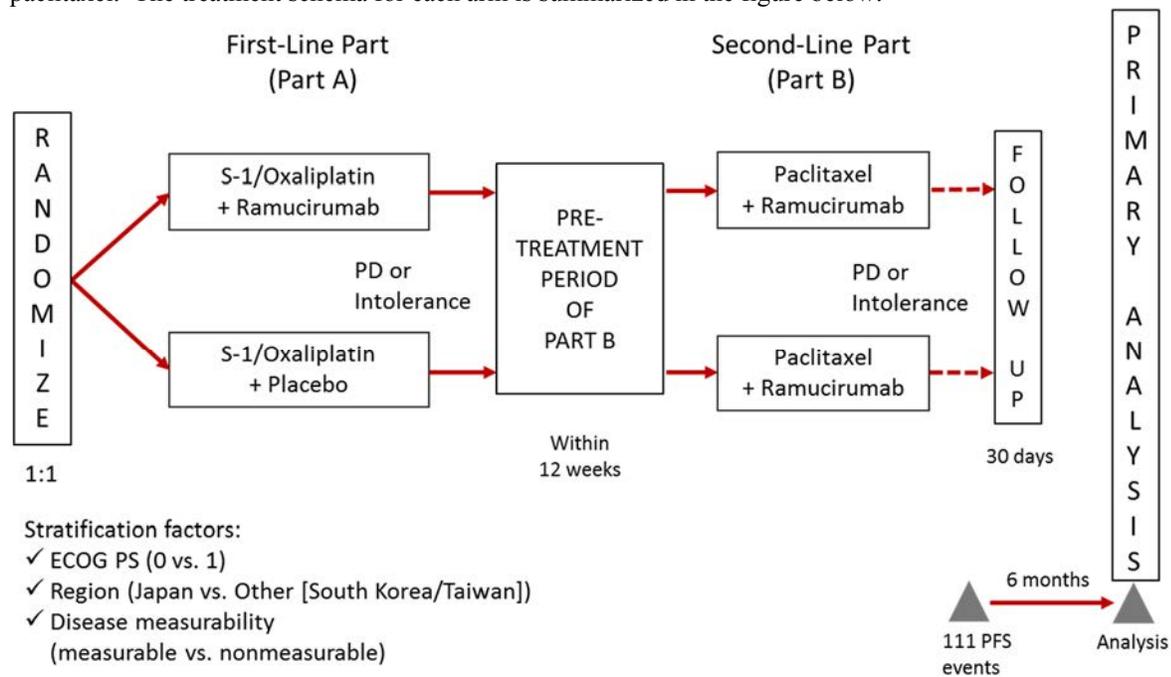
Abbreviations: ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; PFS = progression-free survival; PS = performance status.

Diagnosis and Main Criteria for Inclusion and Exclusions: Eligible patients are required to: (1) have a histopathologically or cytologically confirmed diagnosis of gastric or GEJ adenocarcinoma (patients with esophageal cancer are not eligible); (2) have measurable or nonmeasurable but evaluable disease determined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; (3) have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (4) have adequate organ function and (5) have an estimated life expectancy of $\geq$12 weeks. Patients must not have received any prior first-line systemic treatment (prior adjuvant or neo-adjuvant therapy is permitted), or have human epidermal growth factor receptor 2 (HER2)-positive status (patients with a negative test or having an indeterminate result due to any reason are eligible, provided these patients are not eligible for treatment directed against tumors which overexpress HER2).

LY3009806

Investigational Product, Dosage, and Mode of Administration:
Part A (21 days/cycle)

- Ramucirumab: supplied in sterile preservative-free single-use vials containing 500 mg/50 mL product, at a final concentration of 10 mg/mL in a histidine-buffered formulation, administered as an I.V. infusion at a dose of 8 mg/kg on Day 1 and Day 8. The infusion should be delivered over approximately 60 minutes. The infusion rate should not exceed 25 mg/min.
- Placebo: supplied in single-use 50-mL vials containing histidine buffer only. Because investigators and ancillary medical personnel will be blinded as to assignment to active therapy versus placebo, the volume of placebo to be administered will be calculated as if it were active product formulated at 10 mg/mL (with a dose of 8 mg/kg). Placebo will be administered as an I.V. infusion on Day 1 and Day 8.

Part B (28 days/cycle)

- Ramucirumab: supplied in sterile preservative-free single-use vials containing 500 mg/50 mL product, at a final concentration of 10 mg/mL in a histidine-buffered formulation, administered as an I.V. infusion at a dose of 8 mg/kg on Day 1 and Day 15. The infusion should be delivered over approximately 60 minutes. The infusion rate should not exceed 25 mg/min.

Reference Therapy, Dose, and Mode of Administration:
Part A (21 days/cycle)

- S-1: 80-120 mg/day on Days 1-14 administered orally (Note: dose of S-1 is determined by body surface area).
- Oxaliplatin: 100 mg/m^2 on Day 1 as an I.V. infusion.

Part B (28 days/cycle)

- Paclitaxel: administered as an I.V. infusion at a dose of 80 mg/m^2 on Day 1, Day 8 and Day 15.

Planned Duration of Treatment: Patients will continue to receive study treatment until there is radiographic or symptomatic progression of disease, toxicity requiring cessation, withdrawal of consent, or until other withdrawal criteria are met.

Baseline period (Part A): 3 weeks

Treatment period (Part A): A treatment cycle will be defined as a period of 21 (±3) days.

Pre-treatment period of Part B (Part B): After discontinuation of treatment in Part A, the pre-treatment period of Part B will be started and patients who meet initiation criteria of Part B can start administration of study treatment of Part B. Patients who do not meet initiation criteria of Part B within 12 weeks from decision of study treatment discontinuation of Part A should be discontinued from the study.

Treatment period (Part B): A treatment cycle will be defined as a period of 28 (±3) days.

Short-term follow-up for safety (postdiscontinuation): Patients who will start a treatment other than Part B treatment must be followed for 30 days (±7 days) after the decision is made that the patient will not move to Part B (eg, the patient who do not meet initiation criteria of Part B within 12 weeks from decision of study treatment discontinuation of Part A) or no longer continue study treatment of Part B.

Long-term follow-up (postdiscontinuation):

- Patients who discontinue for reasons other than radiographically documented progressive disease (PD) will continue tumor assessment every 6 weeks (±7 days) as calculated from randomization for the first year, and every 9 weeks ±7 days thereafter until radiographically documented PD, death, or study completion except when not feasible in the opinion of the investigator due to patient's clinical status.
- Follow-up for the collection of survival data and subsequent anticancer treatments should be attempted after discontinuation of study treatment at regularly scheduled intervals (every 12 weeks ± 14 days) until study completion or death, whichever occurs first.

LY3009806

Criteria for Evaluation:

Efficacy: PFS (until first PD), PFS2 (until second PD), OS, ORR, and DCR

Safety: Adverse events (AEs), serious adverse events (SAEs), electrocardiograms (ECGs), vital signs, and laboratory analyses

Pharmacokinetics: Pharmacokinetic parameters including, but not limited to: calculation of mean serum ramucirumab concentrations prior to infusion (minimum concentration [C_{min}]). These will be performed on all patients at baseline, specified time points during treatment, the pre-treatment period of Part B, the short-term safety follow-up visit, and in the event of an infusion-related reaction (IRR; as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event).

Immunogenicity: Serum samples will be analyzed for antibodies to ramucirumab on all patients at baseline, specified time points during treatment, the pre-treatment period of Part B, the short-term safety follow-up visit, and in the event of an IRR (as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event).

Statistical Methods:
The study will enroll approximately 190 patients in 1:1 randomization and the primary endpoint analysis will be performed 6 months after observing 111 PFS events. The expected number of PFS events at this time point is 136 and the probability of having a 2-sided p-value of less than 0.2 (correspond to 1-sided 0.1) using a log-rank test in terms of PFS would be approximately 85%, assuming the recruitment rate of 8 patients per month, the hazard ratio (HR) of 0.67 (median 6 months vs. 9 months) and approximately 10% of enrolled patients would be censored before the data cut-off. The probability of having a 2-sided p-value of less than 0.2 with 111 events under the same assumption would be 80%.

Efficacy:
The primary efficacy analysis will be performed on the full analysis set (FAS), consisting of all randomized patients receiving any quantity of study treatment for Part A and grouped according to the treatment the patients were assigned. The primary analysis will compare the PFS between the 2 treatment groups (with vs. without ramucirumab) using a stratified log-rank test and estimation of HR using a stratified Cox regression model. Stratification will be based on the same stratification factors included in the randomization. In addition, estimation of within-arm survival parameters for the 2 treatment groups will be generated using the Kaplan-Meier method.

Other time-to-event efficacy endpoints (OS, PFS2) will be analyzed in analogous fashion. Objective response rate (complete response [CR]+ partial response [PR]) and its confidence interval will be reported.

Safety:
Safety summaries will be provided separately for Part A and Part B. The safety population (SP) will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety population for Part B study treatment (SP2) will include all patients who received any quantity of study treatment for Part B. The safety evaluation will be performed based on the actual study treatment a patient has received, regardless of the treatment arm to which he or she was randomized. The safety population for Part B ramucirumab (SP3) will include all patients who received any quantity of ramucirumab for Part B. The safety evaluation will be performed based on the actual ramucirumab treatment a patient received, regardless of the treatment arm to which he or she was randomized. Safety analyses will include summaries of the incidences of AEs by maximum the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade (Version 4.03) that occur during the study treatment period or within approximately 30 days after the decision is made to discontinue study treatment. Additionally, the following safety-related outcomes will be summarized:
- study treatment discontinuations due to AEs
- deaths during the study treatment period or within 30 days after the decision is made to discontinue study treatment
- SAEs during the study treatment period or within 30 days after the decision is made to discontinue study treatment
- hospitalizations and transfusions during the study treatment period or within 30 days after the decision is made to discontinue study treatment

Pharmacokinetics /Immunogenicity: Serum ramucirumab concentrations and incidence of anti-ramucirumab antibodies will be tabulated.

Translational Research: Plasma, whole blood, and tumor tissue (optional) will be examined for markers related to pathways associated with gastric/GEJ adenocarcinoma, the mechanism of action of ramucirumab, S-1, oxaliplatin, and/or angiogenesis, and will also be used for related research methods or validation of diagnostic tools and/or assays. Plasma, whole blood, and tumor tissue (optional) will not be used for broad exploratory unspecified disease or population genetic analysis.

3. Table of Contents

A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

List of Tables

List of Figures

List of Attachments

4. Abbreviations and Definitions

Term	Definition
5-FU	5-fluorouracil
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
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
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, good clinical practice, and the applicable regulatory requirement(s).
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until database lock for the primary endpoint analysis.
	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not.
	A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BSC	best supportive care
CapeOX	capecitabine+oxaliplatin
$C_{ave,ss}$	average concentration at steady state
CHF	congestive heart failure
CI	confidence interval

CIOMS	Council for International Organizations of Medical Sciences
$C_{max,ss}$	maximum concentration at steady state
C_{min}	minimum concentration
$C_{min,1}$	minimum concentration after first dose administration
$C_{min,ss}$	minimum concentration at steady state
collection database	A computer database where clinical trial data are entered and validated.
CR	complete response
eCRF	electronic 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.
CRS	clinical research scientist
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.
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DCR	disease control rate
DCR2	disease control rate of second-line therapy
DVT	deep vein thrombosis
ECF	epirubicin+cisplatin+5-fluorouracil
ECG	electrocardiogram
ECX	epirubicin+cisplatin+capecitabine

ECOG	Eastern Cooperative Oncology Group
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
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 directly.
EOF	epirubicin+oxaliplatin+5-fluorouracil
EOX	epirubicin+oxaliplatin+capecitabine
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.
FAS	full analysis set
FAS2	full analysis set for Part B
FDA	Food and Drug Administration
FOLFIRI	irinotecan, folinic acid, and 5-fluorouracil
GEJ	gastroesophageal junction
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestinal
GPS	Global Patient Safety
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ILD	interstitial lung disease
IMCL	ImClone

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.
investigational product (IP)	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when:

      1. used or assembled (formulated or packaged) in a way different from the authorized form,

      2. used for an unauthorized indication, or

      3. used to gain further information about the authorized form.

      In this study, the IP is ramucirumab/placebo.

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.
IRR	infusion-related reaction
I.V.	intravenous
IWRS	interactive web response system
JGCA	Japan Gastric Cancer Association
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
mFOLFOX-6	modified FOLFOX-6 (oxaliplatin, 5-fluorouracil, and leucovorin)
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
ORR	objective response rate
ORR2	objective response rate of second-line therapy

LY3009806

OS	overall survival
OS2	overall survival of second-line therapy
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival 2
PFS2-1	progression-free survival of second-line therapy
PK	pharmacokinetic(s)
PIGF	placental growth factor
PPS	per protocol set
	The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PR	partial response
PS	performance status
PTT/aPTT	partial thromboplastin time/activated partial thromboplastin time
QTc	corrected QT
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors
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	The process of screening a patient who was previously declared a screen failure for the same study
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAP	statistical analysis plan

LY3009806

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 (eg, diagnostic CT/MRI, blood draws).
screen failure	patient who does not meet one or more criteria required for participation in a trial
SOX	S-1+oxaliplatin
SP	safety population
SP2	safety population for Part B study treatment
SP3	safety population for Part B ramucirumab
Study completion	This study will be considered complete when the primary endpoint analysis (6 months after observing 111 PFS events) has been performed and evaluated and sufficient OS-related information is collected for analysis, as determined by the Sponsor
SUSAR	suspected unexpected serious adverse reaction
sVEGF	soluble vascular endothelial growth factor
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.
TPO	third-party organization
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event

A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

5. Introduction

5.1. Gastric Cancer

5.1.1. Background

In 2012, the world age-standardized incidence rate of gastric cancer across all geographies for which estimates are available was 17.4 per 100,000 males and 7.5 per 100,000 females (IARC [WWW]). Overall, gastric cancer is the second most common cause of cancer-related death worldwide (Van Cutsem et al. 2006), with associated age-adjusted mortality rates of 12.8 per 100,000 and 5.7 per 100,000 among males and females, respectively (IARC [WWW]). Gastric cancer is most prevalent in East Asia. In Japan, gastric cancer is the second most frequently diagnosed cancer, and the second leading cause of cancer deaths, with an estimated 125,730 new cases in 2010 and 48,632 cancer deaths in 2013 (Japan Ministry of Health, Labour and Welfare [WWW]). In South Korea, gastric cancer is the third most frequently diagnosed cancer, and the third leading cause of cancer deaths, with an estimated 31,269 new cases and 10,746 cancer deaths in 2012 (IARC [WWW]). In Taiwan, gastric cancer is the eighth most frequently diagnosed cancer, and the sixth leading cause of cancer deaths, with an estimated 3796 new cases in 2012 and 2386 cancer deaths in 2012 (Taiwan Cancer Registry Annual Report, 2012).

5.1.2. First-Line Chemotherapy in Gastric Cancer

While surgical resection is the preferred approach for treatment of gastric cancer, approximately two-thirds of patients present with disease that is advanced or metastatic at diagnosis (Vanhoefer et al. 2000). For such patients, the prognosis is limited; the median survival for patients with untreated metastatic gastric cancer is from 3 to 5 months (Murad et al. 1993; Pyrhonen et al. 1995; Glimelius et al. 1997).

In Japan, a large proportion of gastric cancer is diagnosed in the early stage because of screening programs and early access to endoscopy (Sasako et al. 2010); however, one-sixth of patients are still diagnosed with advanced inoperable gastric cancer (Report of Hospital-Based Cancer Registry [WWW]). For such patients, systemic chemotherapy is the mainstay of treatment for advanced and metastatic gastric cancer (JGCA 2010; NCCN Clinical Practice Guidelines in Oncology [WWW]). Combination chemotherapy regimens, particularly those containing fluoropyrimidines and platinum-based agents, has been recommended in the guidelines as first-line systemic chemotherapy for advanced gastric cancer (JGCA 2010; NCCN Clinical Practice

Guidelines in Oncology [WWW]). S-1 is an orally active combination of tegafur (a prodrug of 5-fluorouracil [5-FU]) with gimeracil and oteracil (PMDA [WWW]). In the 2014 Japan Gastric Cancer Association (JGCA) guideline, the combination of S-1 and cisplatin was established as the first choice for first-line systemic chemotherapy for human epidermal growth factor receptor 2 (HER2)-negative gastric cancer (JGCA 2010), based on the SPIRITS trial (Koizumi et al. 2008). The combination of capecitabine and cisplatin is another first-line systemic chemotherapy regimen that has been effective against HER2-negative gastric cancer (JGCA 2010). For HER2-positive gastric cancer, the combination of capecitabine and cisplatin+trastuzumab is recommended in the guideline based on the trastuzumab for gastric cancer trial (Bang et al. 2010); S-1 and cisplatin+trastuzumab is also described as an option.

Since September 2014, oxaliplatin has been available in Japan (JGCA [WWW]). Two oxaliplatin-based treatment regimens, capecitabine+oxaliplatin (CapeOX) (Doi et al. 2010) and S-1+oxaliplatin (SOX) (Koizumi et al. 2010; Yamada et al. 2013, 2015), are now available in Japan (JGCA [WWW]).

In South Korea and Taiwan, CapeOX and SOX regimens are also available for first-line systemic chemotherapy (Shen et al. 2013).

5.1.3. Ramucirumab

5.1.3.1. Background

Pathways that mediate angiogenesis are considered important targets in cancer drug development. Vascular endothelial growth factors (VEGFs; including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor) have emerged as key regulators of angiogenesis, and the expression of VEGFs has been correlated with poor prognosis in several solid tumor types, including gastric adenocarcinoma (Roy et al. 2006; Amini et al. 2012; Oh et al. 2013; Xie et al. 2013). Ramucirumab is a human receptor-targeted antibody that specifically binds VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands VEGF-A, VEGF-C, and VEGF-D (Lu et al. 2003; Zhu et al. 2003; Report IMC04). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2, thereby inhibiting ligand-induced proliferation, downstream signaling components including Erk1/Erk2, and migration of human endothelial cells (Lu et al. 2003; Zhu et al. 2003; Jimenez et al. 2005; Miao et al. 2006; Goldman et al. 2007; Tvorogov et al. 2010). Preclinical data for DC101, a neutralizing rat anti-mouse monoclonal antibody specific for murine VEGF Receptor-2, demonstrated antitumor activity in multiple tumor models.

A comprehensive clinical development program to assess ramucirumab in the treatment of solid tumor malignancies was initiated following Phase 1 studies evaluating dose, schedule, and toxicity. The clinical development has focused on tumors where VEGF ligands (including VEGF-A) and VEGF Receptor 2 are overexpressed and where the unmet medical need is high (Roy et al. 2006; Seto et al. 2006; Andersen et al. 2009; Jantus-Lewintre et al. 2011; Amini et al. 2012; Oh et al. 2013).

5.1.3.2. Early Development

Several factors provided rationale for further clinical development in gastric cancer; these include the contribution of angiogenesis to cancer pathogenesis, preclinical evaluations of the rat antibody to murine VEGF Receptor 2, DC101 (ramucirumab does not cross react with the murine VEGF Receptor 2; therefore, DC101 was used in murine models as a proof-of-principle surrogate antibody) in gastric cancer models, and preliminary evidence of potential activity of other antiangiogenic agents in gastric cancer (Jung et al. 2002; Enzinger et al. 2006; Shah et al. 2006).

Clinical activity was seen early in the development of ramucirumab. In Phase 1 studies, ramucirumab was generally well tolerated and exhibited preliminary evidence of anti-tumor activity in patients with solid tumors. The maximum tolerated dose (MTD) of ramucirumab was identified as 13 mg/kg when given once weekly in the Phase 1 dose-escalation Study I4T-IE-JVBM (JVBM; ImClone [IMCL] CP12-0401). Preliminary activity was observed across a range of doses, including the 2-mg/kg weekly dose. Every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study, I4T-IE-JVBN (JVBN; IMCL CP12-0402). No MTD was identified for every-2-week or every-3-week dosing; all dose regimens were well tolerated, and preliminary evidence of clinical efficacy was observed across a range of dose/schedule cohorts.

5.1.3.3. Clinical Development in Gastric Cancer

At the time of this protocol, ramucirumab has been approved for patients with advanced or metastatic, gastric or gastroesophageal junction (GEJ) adenocarcinoma in the United States, the European Union, and Japan (CYRAMZA package insert, 2014).

The approval of ramucirumab as a single agent was based on clinical efficacy and safety demonstrated in the randomized Phase 3 study REGARD (I4T-IE-JVBD; IMCL CP12-0715), which compared ramucirumab monotherapy with best supportive care (BSC) in patients with advanced gastric or GEJ adenocarcinoma whose disease had progressed after prior chemotherapy (N=355) (Fuchs et al. 2014). Median overall survival (OS) was 5.2 months in the ramucirumab arm versus 3.8 months in the placebo arm (hazard ratio [HR]=0.776, 95% confidence interval [CI]: 0.603, 0.998; p=.047). Ramucirumab was well tolerated in this patient population, with similar rates for most adverse events (AEs) between treatment arms. Rates of hypertension were higher in the ramucirumab arm than in the placebo arm (38 [16%] patients vs. 9 [8%] patients, respectively), whereas rates of other AEs were mostly similar between the ramucirumab arm and the placebo arm (223 [94%] patients vs. 101 [88%] patients, respectively). Five (2%) deaths in the ramucirumab arm and 2 (2%) deaths in the placebo arm were considered to be related to study drug.

The approval of ramucirumab in combination with paclitaxel in patients with advanced gastric or GEJ cancer whose disease had progressed after prior platinum/fluoropyrimidine-based chemotherapy was based on the randomized Phase 3 study RAINBOW (I4T-IE-JVBE; IMCL CP12-0922) (N=665) (Wilke et al. 2014). The primary endpoint of OS was met; median OS was 9.63 months in the ramucirumab plus paclitaxel arm compared with 7.36 months in the placebo plus paclitaxel arm (HR=0.807, 95% CI: 0.678, 0.962; p=.0169). Grade ≥3 AEs occurring in

>5% of patients in the ramucirumab plus paclitaxel arm were: neutropenia (40.7% in the ramucirumab plus paclitaxel arm vs. 18.8% in the placebo plus paclitaxel arm), leukopenia (17.4% vs. 6.7%), hypertension (14.1% vs. 2.4%), anemia (9.2% vs. 10.3%), fatigue (7.0% vs. 4.0%), abdominal pain (5.5% vs. 3.3%), and asthenia (5.5% vs. 3.3%). Febrile neutropenia was reported in 3.1% of patients in the ramucirumab plus paclitaxel arm and 2.4% of patients in the placebo plus paclitaxel arm.

A recently completed randomized, placebo-controlled, double-blind, Phase 2 study of ramucirumab in combination with mFOLFOX-6 (modified FOLFOX-6 [oxaliplatin, 5-FU, and leucovorin]) as first-line therapy for advanced adenocarcinoma of the esophagus, GEJ, or stomach (N=168) (I4T-MC-JVBT [JVBT; IMCL CP12-0918]) showed no improvement in the primary endpoint (progression-free survival [PFS]) (median PFS was 6.4 months for the ramucirumab arm vs. 6.7 months for the placebo arm; stratified HR=0.98, 95% CI: 0.69, 1.37; p=.886), or the secondary OS endpoint (median OS was 11.7 months for the ramucirumab arm vs. 11.5 months for the placebo arm; stratified HR=1.08, 95% CI: 0.73, 1.58; p=.712), but did lead to an improved PFS rate at 3 months (89.0% for the ramucirumab arm vs. 75.3% for the placebo arm) and an improved disease control rate (DCR) (84.5% for the ramucirumab arm vs. 66.7% for the placebo arm; p=.008). The majority of patients had a primary tumor location at initial diagnosis of GEJ/cardia/esophagus (76.8%), with nearly half of the patients (47.6%) having a primary tumor location of esophagus. Progression-free survival was similar for all subgroups pairings with the exception of primary tumor location. In a preplanned subgroup analysis, an improvement in PFS (as assessed by HR) was observed for ramucirumab in patients with a primary tumor location of gastric/GEJ/cardia (median PFS was 8.7 months for the ramucirumab arm vs. 7.1 months in the placebo arm; HR=0.77) compared to patients with a primary tumor location of esophagus (median PFS was 5.6 months for the ramucirumab arm vs. 6.1 months for the placebo arm; HR=1.30). A higher rate of discontinuation from study treatment for reasons other than progressive disease (PD) was observed in the ramucirumab arm compared with the placebo arm (50% vs. 19%, respectively), which led to lower study drug exposure in the ramucirumab arm. These observations may have had a negative impact on the results of the PFS assessment of the entire study population. Overall, the safety profile for ramucirumab in this study was consistent with the known safety profile of ramucirumab. The most common Grade ≥3 AE (by consolidated AE) reported was neutropenia (26.8% in the ramucirumab arm vs. 36.3% in the placebo arm). Fatigue (18.3% vs. 15.0%, respectively) and neuropathy (8.5% vs. 11.3%, respectively) were the most common Grade ≥3 AEs (by consolidated term) reported at a similar frequency in the ramucirumab arm compared to the placebo arm. The following treatment-emergent adverse events (TEAEs) (by consolidated term) were reported more frequently (≥5% greater) in the ramucirumab arm than in the placebo arm, respectively: thrombocytopenia (56.1% vs. 38.8%), headache (23.2% vs. 15.0%), hypokalemia (19.5% vs. 8.8%), hypocalcaemia (9.8% vs. 2.5%), and hypophosphatemia (7.3% vs. 1.3%). Grade ≥3 adverse events of special interest (AESIs) were uncommon, with the exception of hypertension (15.9% in the ramucirumab arm vs. 3.8% in the placebo arm).

Together, these results provide justification of further study of ramucirumab in the first-line gastric cancer setting.

More information about the known and expected benefits, risks, and reasonably anticipated AEs of ramucirumab 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 the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

5.2. Rationale for Selection of Ramucirumab Dose Regimen (8 mg/kg on Day 1 and Day 8 Every 21 Days)

Study I4T-JE-JVCW (JVCW) will examine ramucirumab at a dose of 8 mg/kg on Day 1 and Day 8 on an every-21-day (3-week) schedule for Part A. In previous trials conducted in a second-line setting, ramucirumab was administered at a dose of 8 mg/kg every 2 weeks (REGARD) and 8 mg/kg on Day 1 and Day 15 in a 28-day schedule (RAINBOW). Dose selection for Study JVCW is based on information obtained from exposure-response analyses in REGARD and RAINBOW.

Efficacy

Exposure-efficacy response analyses performed on data obtained from REGARD and RAINBOW demonstrated that an increase in exposure is associated with improvement in efficacy in terms of both OS and PFS.

In REGARD, patients with greater-than-median ramucirumab exposure demonstrated significantly longer OS and PFS (smaller HR) as compared to patients with less-than-median ramucirumab exposure.

In RAINBOW, patients with ramucirumab exposure greater-than-the-median were associated with significantly longer OS and PFS (smaller HR) as compared to patients with ramucirumab exposure lower-than-the-median.

These findings were consistent for all 4 exposure measures tested: minimum concentration after first dose administration ($C_{min,1}$), minimum concentration at steady state ($C_{min,ss}$), maximum concentration at steady state ($C_{max,ss}$), and average concentration at steady state ($C_{ave,ss}$).

Safety

Weekly doses of ramucirumab ranging from 2 mg/kg to 16 mg/kg were evaluated in the Phase 1 Study JVBM. An MTD for weekly dosing was identified as 13 mg/kg. Every-2-week (6 mg/kg to 10 mg/kg) and every-3-week (15 mg/kg to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study (Study JVBN). All dose regimens in Study JVBN were well tolerated and no MTD was identified in this study.

REGARD demonstrated a well-tolerated safety profile in the gastric cancer monotherapy setting. Due to the low incidence of hypertension and neutropenia, no safety-exposure relationship was identified.

In RAINBOW, the overall safety profile was also considered manageable, although increasing ramucirumab exposure was correlated with increased incidence of Grade 3 or greater hypertension, neutropenia, and leukopenia. Of note, no Grade 4 or 5 hypertension events were observed in RAINBOW. Hypertension was managed primarily by the use of standard antihypertensive medication, and the association of neutropenia with ramucirumab exposure did not appear to translate to an increased risk of febrile neutropenia with higher ramucirumab exposure.

Conclusions

These data indicated that there may be an opportunity to further improve ramucirumab activity in the gastric indication. Based on pharmacokinetic (PK) simulation, a dose regimen of 8 mg/kg on Day 1 and Day 8 every 21 days (3 weeks) was selected for Study JVCW. This dose regimen is compatible with the 21-day S-1+oxaliplatin dosing schedule. More importantly, this dose regimen may produce a $C_{min,ss}$ greater than the median $C_{min,ss}$ obtained from the standard 8-mg/kg every-2-week regimen in at least 70% of the patient population (Figure JVCW.5.1), and therefore may produce better clinical efficacy outcomes relative to the 8-mg/kg every-2-week regimen. The ramucirumab-related safety risk in the gastric cancer indication may not be significantly increased using the selected dose of 8 mg/kg on Day 1 and Day 8 every 21 days, since the selected dose for Study JVCW is still approximately 60% lower than the maximum tolerated weekly dose identified in the Phase 1 dose-escalation Study JVBM (13 mg/kg weekly).

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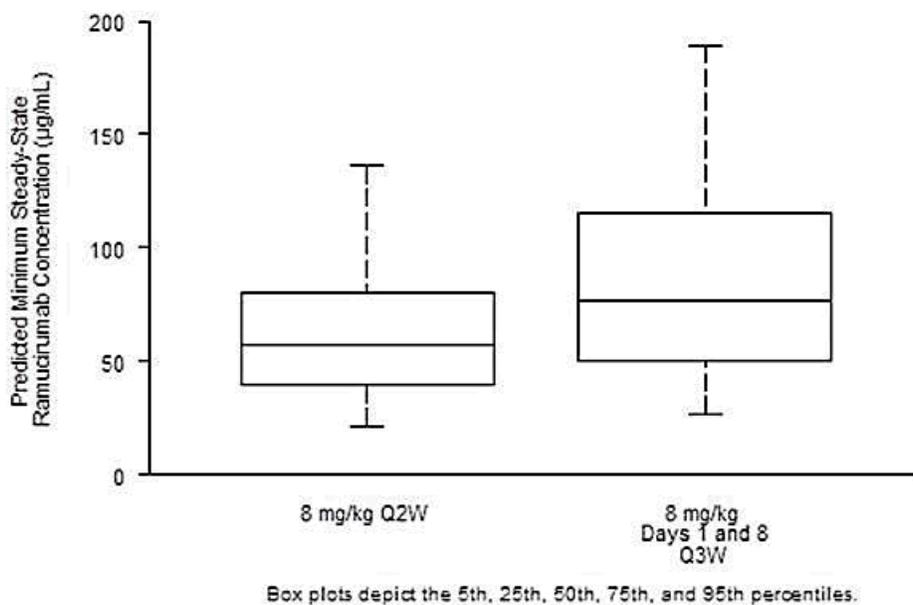
Abbreviations: $C_{min,ss}$ = minimum concentration at steady state; Q = every; W = week. Box plots depict the 5th, 25th, 50th, 75th, and 95th percentiles calculated from 1000 simulation iterations.

Figure JVCW.5.1.   Predicted $C_{min,ss}$ following different dose regimens.

The tolerability of ramucirumab at a dose of 8 mg/kg on Day 1 and Day 8 on an every-21-day (3-week) schedule in combination with S-1 and oxaliplatin will be evaluated in a Japan Phase 1 study (I4T-JE-JVCX) before starting enrollment of Study JVCW.

5.3. Study Rationale

As described in Section 5.1.2, the median survival for patients with untreated metastatic gastric cancer is from 3 to 5 months. Recent developments have focused on the addition of targeted biologic agents to standard chemotherapy in an effort to improve clinical outcome.

Inhibition of angiogenesis has been clinically validated in oncology, with approval of medications targeting the VEGF-A ligand, VEGF Receptor 2, or receptor tyrosine kinases. The feasibility of administering ramucirumab in the gastric cancer setting has been demonstrated in the global, randomized, double-blind Phase 3 REGARD and RAINBOW studies. These studies met their primary endpoint of OS, demonstrating statistically significant and clinically meaningful improvements with ramucirumab that was supported by a highly statistically significant improvement in PFS (see Section 5.1.3.3). The safety profile of single-agent ramucirumab in the pivotal Phase 3 REGARD trial was favorable, with an AE profile that was similar to placebo. The safety profile of ramucirumab in combination with paclitaxel in the pivotal Phase 3 RAINBOW trial demonstrated that the combination was well tolerated in patients with gastric cancer, with manageable AEs.

Additional support of ramucirumab in the first-line setting is provided by a Phase 2 study of ramucirumab in combination with mFOLFOX-6 (Study JVBT) for advanced adenocarcinoma of the esophagus, GEJ, or stomach. As discussed in Section 5.1.3.3, though the combination did not improve median PFS, the addition of ramucirumab did lead to an improved PFS rate of 3 months and an improved DCR. In addition, a longer median PFS and numerically favorable HR were observed in the ramucirumab arm for the subgroup of patients with a primary tumor location of gastric/GEJ/cardia. Furthermore, the overall safety profile for ramucirumab in this study was consistent with the known safety profile of ramucirumab.

The choice of the S-1 and oxaliplatin chemotherapy backbone in Study JVCW is based on previous Phase 3 studies REAL-2 and G-SOX, which have shown this combination to be an acceptable standard first-line regimen for metastatic gastric cancer. In addition, this combination is considered an acceptable standard per Japan local guidelines (JGCA [WWW]).

1) REAL-2 Study

The REAL-2 study was designed 2 x 2 to validate the non-inferiority for replacing cisplatin with oxaliplatin and 5-FU with capecitabine against epirubicin+cisplatin+5-FU (ECF) therapy, which had been considered until then, mainly in Europe, as standard therapy for unresectable advanced or recurrent gastric cancer. The non-inferiority of oxaliplatin versus cisplatin was validated by comparing 2 combined treatment arms of ECF (n=249) with epirubicin+cisplatin+capecitabine (ECX) (n=241) and epirubicin+oxaliplatin+5-FU (EOF) (n=235) with epirubicin+oxaliplatin+capecitabine (EOX) (n=239). The median OS, which was the primary endpoint, was 10.0 months in the cisplatin arm and 10.4 months in the oxaliplatin arm (HR=0.92

[95% CI 0.80-1.10]). The presetting non-inferiority margin 1.23 was cleared and the non-inferiority of oxaliplatin against cisplatin was validated.

2) G-SOX Study

The G-SOX study was designed to validate the non-inferiority of SOX therapy against S-1 plus cisplatin therapy, which is the standard therapy in Japan. The primary endpoints were PFS and OS. A total of 685 patients (343 patients in S-1 plus cisplatin therapy and 342 patients in SOX therapy) were enrolled. The frequency of Grade 3/4 AEs (except for sensory neuropathy in the safety analysis group) for patients in SOX therapy tended to be lower than for those in S-1 plus cisplatin therapy; also, Grade 3/4 thrombocytopenia was 10.1%, which was the equivalent value as S-1 plus cisplatin therapy. However, regarding efficacy, the non-inferiority was validated to analyze the Pre-Protocol set (S-1 plus cisplatin arm 324 patients and SOX arm 317 patients) and the median OS was 13.1 months in the S-1 plus cisplatin arm and 14.1 months in the SOX arm (HR=0.969 [95% CI 0.812-1.157]). This slightly exceeded the non-inferiority margin upper limit of 1.15 set beforehand, and failed to statistically validate the non-inferiority (p=.0583) (Higuchi et al. 2013; Goto 2014). However, the point estimation of HR was also 0.969 in this study and, considering that all other clinical studies comparing oxaliplatin and cisplatin (including the REAL-2 study) also reported HRs <1, it can also be noted that the G-SOX study achieved a consistent result.

Considering the results of the G-SOX study and the high manageability of the therapy, SOX therapy with 100 mg/m^2 should be regarded as a standard of care in gastric first-line therapy in Japan.

Of the available chemotherapy options, S-1 and oxaliplatin are associated with an acceptable toxicity profile, as demonstrated in the REAL-2 and G-SOX studies. Furthermore, considering the safety information provided from a Phase 2 study (I4T-IE-JVBS [JVBS]) of ramucirumab plus mitoxantrone and prednisone in metastatic androgen-independent prostate cancer, in which ramucirumab was administered at 6 mg/kg on Day 1, Day 8, and Day 15 every 21 days, the safety profile of the ramucirumab arm was consistent with the known safety profile of ramucirumab. Based on this information, the increased ramucirumab dose is not expected to significantly increase ramucirumab-related safety risks. Of note, 8 mg/kg on Day 1 and Day 8 every 21 days is lower than the MTD (13 mg/kg/week) identified in Study JVBM, and no MTD was identified for the every-2-week (6 mg/kg to 10 mg/kg) or every-3-week (15 mg/kg to 20 mg/kg) dosing schedules in Study JVBN.

In summary, when available efficacy and safety evidence from REGARD, RAINBOW, Study JVBT, Study JVBS, REAL-2, G-SOX, ramucirumab PK modeling data, and other early phase ramucirumab studies are considered, it is evident that the fluoropyrimidine and platinum combination provides the ideal chemotherapy backbone to evaluate the efficacy and safety of an experimental agent. Additionally, many of these studies involved a third agent, which included conventional therapies as well as targeted antibodies, and the overall safety profile continued to remain clinically manageable, with no significant overlapping toxicities observed. Ramucirumab has also been studied in combination with multiple chemotherapy agents in various solid tumors,

and the safety profile was clinically acceptable. Though an increased rate of neutropenia was observed in RAINBOW, there was no significant increase in the rate of febrile neutropenia. Based on the safety profiles of all agents, overlapping toxicities, if any, are expected to be minimal and clinically manageable.

Based on this evidence, the combination of ramucirumab 8 mg/kg on Day 1 and Day 8 on an every-3-week schedule with S-1 and oxaliplatin has been selected for Study JVCW.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to compare PFS of ramucirumab in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin as first-line treatment in patients with metastatic gastric or GEJ adenocarcinoma.

6.2. Secondary Objectives

Secondary objectives of this study are to assess and compare ramucirumab in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin for the following:

- progression-free survival 2 (PFS2)
- OS
- objective response rate (ORR)
- DCR
- PK of ramucirumab and anti-ramucirumab antibodies (immunogenicity)
- safety and toxicity profile

The definitions of secondary efficacy measures are provided in Section 10.1.4.

6.3. Exploratory Objectives

The exploratory objectives of this study are to assess the following:

- ORR of second-line therapy (ORR2)
- DCR of second-line therapy (DCR2)
- PFS of second-line therapy (PFS2-1)
- OS of second-line therapy (OS2)
- the association between biomarkers and clinical outcome

The definitions of exploratory efficacy measures are provided in Section 10.1.5.

7. Study Population

Re-screening of individuals who do not meet the criteria for participation in this study is not permitted (ie, the individual must not sign a new informed consent form [ICF]). Note that repeating laboratory tests during screening does not constitute re-screening.

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

7.1. Inclusion Criteria

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

[1]   Have a histopathologically or cytologically confirmed diagnosis of metastatic gastric or GEJ adenocarcinoma. Patients with esophageal cancer are not eligible.

[2]   Have not received any prior first-line systemic therapy for gastric or GEJ adenocarcinoma (prior adjuvant or neoadjuvant therapy is permitted). Patients whose disease has progressed after >24 weeks following the last dose of systemic treatment in the adjuvant/neoadjuvant setting are eligible.

[3]   Have measurable or nonmeasurable but evaluable disease determined using guidelines in Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v.1.1; Attachment 7). Baseline tumor assessment should be performed using a high resolution computed tomography (CT) scan using intravenous (IV) and oral contrast unless clinically contraindicated. Magnetic resonance imaging (MRI) is acceptable if a CT scan cannot be performed.

[4]   Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale at baseline (Oken et al. 1982).

[5]   Have adequate organ function, as determined by:

- Hepatic

  Note: the patient should meet all of the following criteria:

  o Total bilirubin ≤1.5 times upper limit of normal (ULN)

  o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x ULN for ALT/AST if no liver metastases, ≤5.0 x ULN if liver metastases.

  o The albumin level must be higher than 2.5 g/dL (or equivalent) measured in a non-dehydrated state.

- Renal: Calculated creatinine clearance must be ≥60 mL/min as determined by either the Cockcroft-Gault formula (see Attachment 6) or 24-hour urinary protein at screening period.

The patient's urinary protein is <2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine or urine protein/creatinine ratio must be collected and must demonstrate <2 g of protein in 24 hours to allow participation in the study.

- Hematologic: Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$, hemoglobin ≥9 g/dL (5.58 mmol/L; packed red blood cell transfusions are not allowed within 1 week prior to baseline hematology profile) and platelets $\geq 100,000/\text{mm}^3$

- Coagulation

  Note: the patient should meet all of the following criteria:

  o International Normalized Ratio (INR) ≤1.5

  o Partial thromboplastin time/activated partial thromboplastin time (PTT/aPTT) ≤1.5 x ULN.

  o Patients receiving warfarin are not eligible for this study.

  o Patients with a venous thrombosis are permitted to enroll provided that they are clinically stable, asymptomatic, and adequately treated with anticoagulation, in the opinion of the investigator.

[6] Is at least 20 years of age at the time of randomization.

[7] Have provided signed informed consent prior to any study-specific procedures and are amenable to compliance with protocol schedules and testing.

[8] Have an estimated life expectancy of ≥12 weeks in the judgment of the investigator.

[9] Eligible patients of reproductive potential (both sexes) must agree to use contraception (hormonal or barrier methods) during the study period and at least 6 months after the last dose of study treatment or longer if required per local regulations.

- For females, a highly effective method of birth control is defined as one that results in a low failure rate (ie, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, or a vasectomized partner. For patients using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.

- Males who are sterile (including vasectomy) or who agree to use a reliable method of birth control and agree to use a reliable method of birth control and agree to not donate sperm during the study and for at least 6 months following the last dose of study treatment or country requirements, whichever is longer, are eligible.

- Females who agree to use a highly effective method of birth control, or are not of childbearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or due to menopause, are eligible. A menopausal female is a female with spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (eg, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy).

[10] Are willing to provide a blood sample for research purposes. Submission of a blood sample is mandatory for participation in this study unless restricted by local regulations or ethical review boards (ERBs); submission of a tumor tissue sample is optional.

7.2. Exclusion Criteria

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

[11] Patients with HER2-positive status as determined per local standards. Patients with a negative test or having an indeterminate result due to any reason are eligible, provided these patients are not eligible for treatment directed against tumors which overexpress HER2.

[12] Patients receiving chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs; eg, indomethacin, ibuprofen, naproxen, or similar agents) or other anti-platelet agents (eg, clopidogrel, ticlopidine, dipyridamole, or anagrelide) within 7 days prior to first dose of study treatment. Aspirin use at doses up to 325 mg/day is permitted.

[13] Have radiation therapy within 14 days prior to randomization. Any lesion requiring palliative radiation or which has been previously irradiated cannot be considered for response assessment.

[14] Have documented brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression.

[15] Have significant bleeding disorders, vasculitis, or have had a significant bleeding episode from the gastrointestinal (GI) tract within 12 weeks prior to randomization.

[16] Have experienced any arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 24 weeks prior to randomization.

[17] Have symptomatic congestive heart failure (CHF; New York Heart Association II-IV) or symptomatic or poorly controlled cardiac arrhythmia.

[18] Have uncontrolled hypertension prior to initiating study treatment, despite antihypertensive intervention.

LY3009806

[19] Have undergone major surgery within 28 days prior to randomization.

[20] Have a history of GI perforation and/or fistulae within 24 weeks prior to randomization.

[21] Have a history of inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤48 weeks prior to randomization.

[22] Have an acute or subacute bowel obstruction or history of chronic diarrhea which is considered clinically significant in the opinion of the investigator.

[23] The patient has:

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

- 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.

[24] Have known allergy, hypersensitivity, or intolerance to any components of study treatment.

[25] Are currently enrolled in, or discontinued study drug within the last 28 days from, a clinical trial involving an investigational product or non-approved use of a drug or device (other than the study drug used in this study), or are 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.

[26] Severely immunocompromised patients (other than that related to the use of corticosteroids) including patients known to be human immunodeficiency virus positive.

[27] Have positive test results for hepatitis B virus (screening is required; documentation of a negative test result within 24 weeks prior to randomization must be available).

A positive test for hepatitis B is defined as:

- positive for hepatitis B surface antigen

AND

- positive for hepatitis B deoxyribonucleic acid

[28] Are pregnant or breast feeding. Females of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to first dose of study treatment.

[29] Have any prior malignancies. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low, as judged by the investigator, in consultation with the Lilly clinical research physician (CRP) or clinical research scientist (CRS), are eligible for this study. The Lilly CRP or CRS will need to approve enrollment of such patients.

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

[31] Have previous or concurrent interstitial lung disease (ILD).

[32] Have difficulties in swallowing oral medication.

7.2.1. Rationale for Exclusion of Certain Study Candidates

The exclusion criteria have been carefully selected by the sponsor to ensure their ethical and scientific acceptability, and to help establish specificity of the patient population for both efficacy and safety analyses.

Exclusion Criteria [24], [26], [27], [30], and [31] are written so that patients with clinical conditions highlighted in these criteria are not inadvertently enrolled as safety concerns with the experimental drug cannot be adequately evaluated. Exclusion Criteria [11] and [29] are written to maintain the specificity of the patient population intended for enrollment and analyses. Exclusion Criteria [12], [15], [16], [17], [18], [19], [20], [21], and [22] are designed to exclude patients known to experience increased or life-threatening toxicities based on the known side effect profile of an antiangiogenic agent such as ramucirumab. Exclusion Criterion [13] is written to ensure patients have adequate time to recover from recent radiotherapy, including the potential risk for radiation-induced myelosuppression. Exclusion Criterion [14] is written to prevent enrollment of patients whose prognosis may be particularly poor. Exclusion Criterion [23] is written to address liver injury as a potential AESI for ramucirumab. Exclusion Criterion [25] is written to prevent recently administered chemotherapy or investigational therapy from confounding an assessment of safety/efficacy in this study. Exclusion Criterion [28] is included due to the lack of experience with use of ramucirumab among females who are either pregnant or breast feeding.

7.3.   Discontinuation

The reason for discontinuation and the date of discontinuation will be collected for all patients who discontinue study treatment or participation from the study. All patients who are randomized and receive any quantity of study treatment and then discontinue, will have procedures performed as shown in the Study Schedule (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.

7.3.1. 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, the sponsor must be notified. If the sponsor 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 sponsor CRP or CRS and the investigator to determine whether the patient may continue in the study, with or without investigational product (IP). Inadvertently enrolled patients may be maintained in the study and on IP when the Lilly CRP or CRS agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without IP if the Lilly CRP or CRS 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 or CRS to allow the inadvertently enrolled patient to continue in the study with or without IP.

7.3.2. Discontinuation of Study Treatment

For discontinuation criteria for study treatment, refer to Sections 9.A.4.1.1, 9.A.4.1.2, 9.A.4.1.3, 9.B.4.1.2, 9.B.4.1.3, and 9.B.4.1.4.

7.3.3. Discontinuation from the Study

Patients will be discontinued from the study drug (ramucirumab/placebo and chemotherapy) and from the study in the following circumstances:

- enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- the investigator decides that the patient should be discontinued from the study
- 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 the study occurs prior to introduction of the new agent
- the patient requests that the patient be withdrawn from the study
- 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).

7.3.4. 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 survival status (ie, alive or dead) for all randomized patients who are lost to follow up within legal and ethical boundaries. Site personnel, or an independent third party, may search public sources for survival

status information. If the patient's survival status is determined, the survival status will be documented and the patient will not be considered lost to follow up.

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

7.3.5. 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, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7.3.6. Discontinuation of the Study

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

8. Investigational Plan

8.1. Summary of Study Design

Study JVCW is a multicenter, randomized, placebo-controlled, double-blind, Phase 2 study of patients with metastatic gastric or GEJ adenocarcinoma. Patients will be randomized to receive ramucirumab (8 mg/kg) in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin (Part A) followed by open-label treatment with ramucirumab plus paclitaxel (Part B).

Figure JVCW.8.1 illustrates the study design.

The study will enroll approximately 190 patients evenly divided between the 2 treatment arms. Primary efficacy analysis will take place 6 months after 111 PFS events have occurred. Randomization will be stratified by ECOG performance status (PS; 0 vs. 1), region (Japan vs. Other [South Korea/Taiwan]), and disease measurability (measurable vs. nonmeasurable). See Section 12.2 for further details.

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; PD = progressive disease; PFS = progression-free survival.
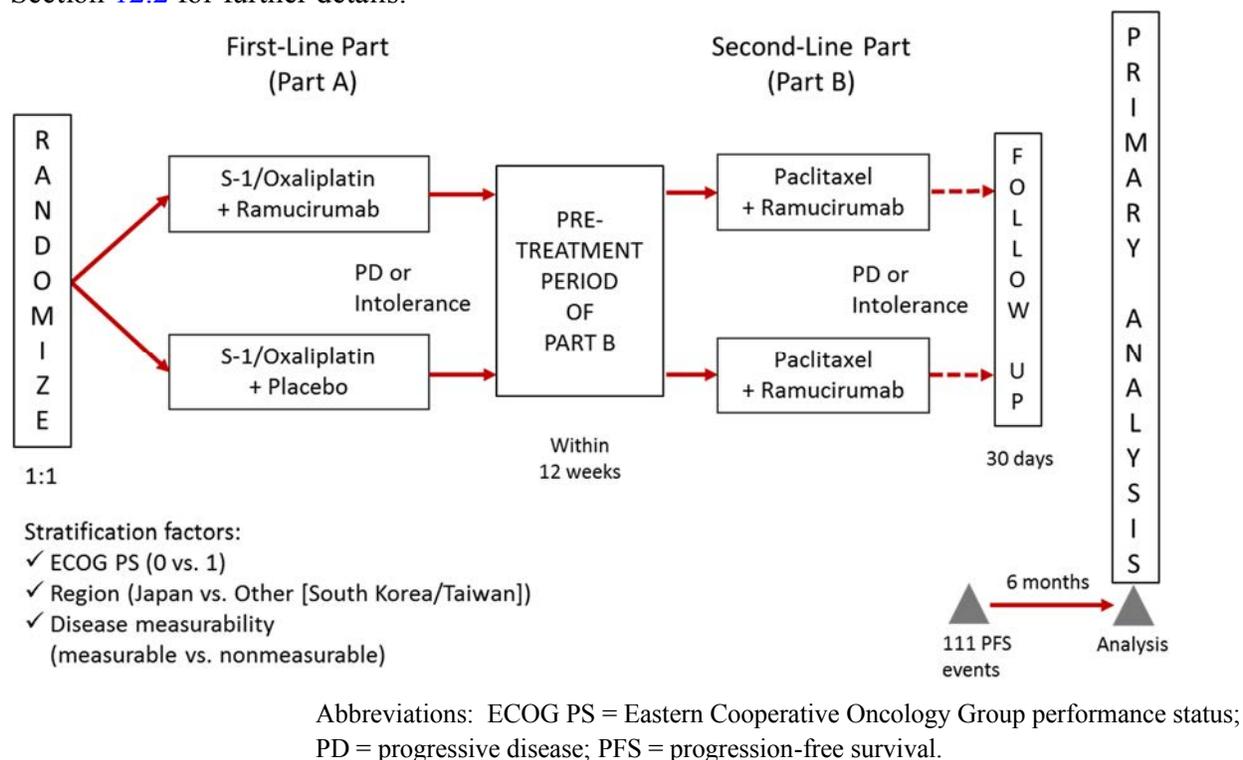
Figure JVCW.8.1.   **Illustration of study design for Protocol I4T-JE-JVCW.**

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

- **Baseline:** begins when the ICF is signed and ends on the day before the day of first dose of study treatment (or discontinuation, if no treatment is given). Patients must be

randomized to treatment within 21 days of signing the ICF, and first treatment will be administered within 7 days following randomization.

- **Treatment Period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue study treatment.
    - *Part A:* a treatment cycle will be defined as a period of 21 (±3) days.
    - *Pre-treatment period of Part B* begins the day after the decision is made that the patient will no longer continue study treatment of Part A.
    - *Part B:* a treatment cycle will be defined as a period of 28 (±3) days.
- **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
    - *Short-term safety follow-up* begins the day after the decision is made that the patient will not move to Part B or no longer continue study treatment of Part B and lasts approximately 30 (±7) days.
    - *Long-term follow-up* begins 1 day after short-term safety follow-up is completed and continues until the patient's death or overall study completion to collect additional data (survival data and subsequent anticancer treatments).
- **Continued Access Period:** begins after primary endpoint analysis has been performed and evaluated, and sufficient OS-related information is collected for analysis, as determined by the Sponsor. 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 (see Section 8.1.5).
    - *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 (±7) days.

Patients will receive I.V. ramucirumab/placebo on Days 1 and 8, every 21 days, in combination with S-1 and oxaliplatin (Part A; Figure JVCW.8.2). Ramucirumab/placebo, S-1, and oxaliplatin will be continued until disease progression, development of unacceptable toxicity, or any other discontinuation criteria are met. Pre-treatment period of Part B begins the day after the decision is made that the patient will no longer continue study treatment of Part A. Patients who meet initiation criteria for Part B will receive I.V. ramucirumab on Days 1 and 15, every 28 days, in combination with paclitaxel (Part B; Figure JVCW.8.2). Patients who do not meet initiation criteria of Part B (see Table JVCW.9.B.9) within 12 weeks from decision of study treatment discontinuation of Part A should be discontinued from study. Blinding of Part A will be kept until database lock (DBL) for the primary endpoint analysis is achieved, even if patients move to Part B or discontinue the study.

Refer to Attachment 1 for the Study Schedule.

First-Line Part (Part A)

Second-Line Part (Part B)
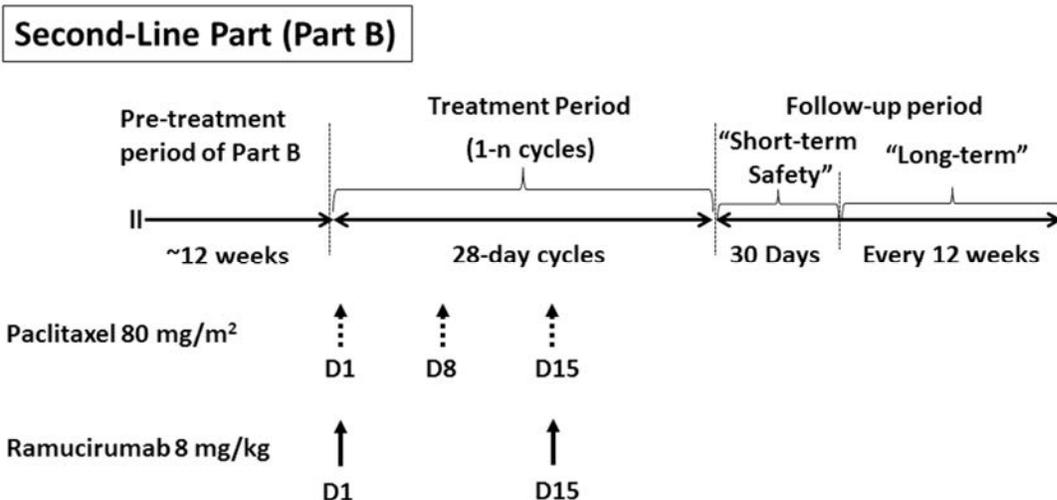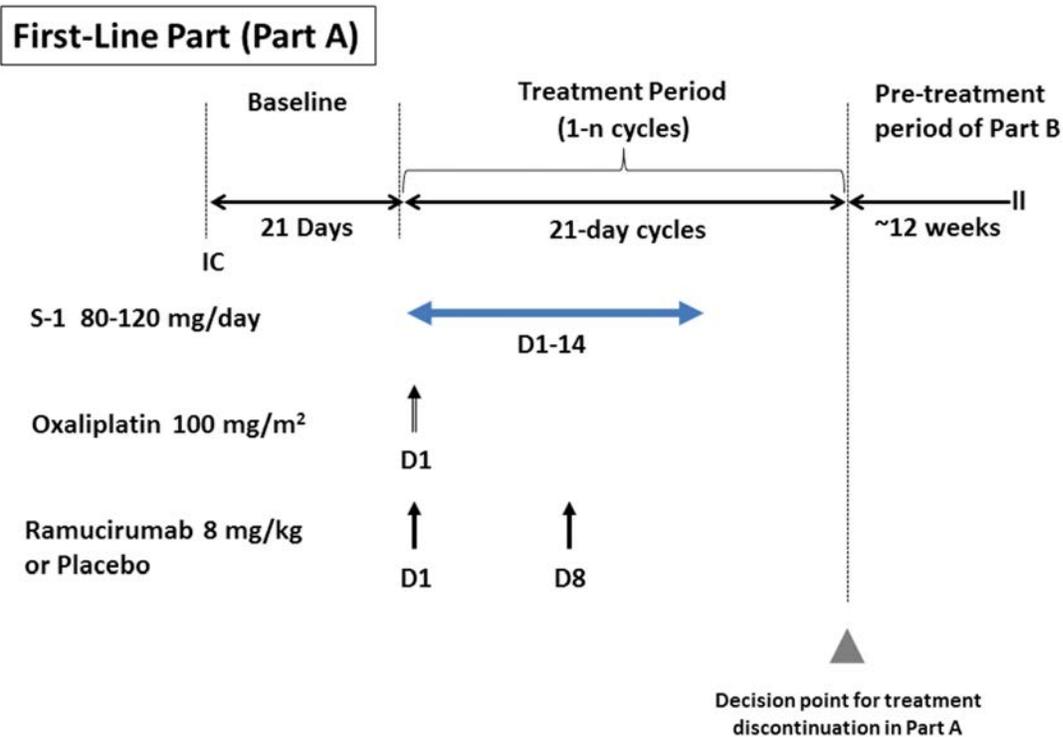
Abbreviations: D = day; IC = informed consent; n = number.

Figure JVCW.8.2.   Illustration of treatment schedule for Part A and Part B.

8.1.1. Baseline and Treatment Period Assessments

Baseline radiographic assessment of disease will be performed within 21 days in Part A and 28 days in Part B prior to first treatment; first treatment will be administered within 7 days following randomization. Patients in both treatment arms will receive any necessary premedication (see Section 9.A.1.1 and Section 9.B.1.1) prior to the infusion of study therapy at each treatment cycle.

A treatment cycle is defined as an interval of 3 weeks (21 days) in Part A and 4 weeks (28 days) in Part B. Administration of all therapeutic products will occur as described in Section 9.A.1 and Section 9.B.1.

Criteria for starting the next cycle and dose reductions of investigational product and/or chemotherapy for specific treatment-related AEs are detailed in Section 9.A.4.1 and Section 9.B.4.1.

For Part A, patients will undergo radiographic assessment of disease status (CT scan or MRI) according to RECIST v 1.1, every 6 weeks (±7 days) from randomization for the first year, and every 9 weeks (±7 days) thereafter, even if treatment is delayed, until there is radiographic documentation of PD. Patients in both treatment arms will be treated until there is radiographic or symptomatic PD, toxicity requiring cessation of treatment, or withdrawal of consent, or until other withdrawal criteria are met. In case of treatment discontinuation for any reason other than radiographically confirmed PD, radiographic tumor assessments will continue every 6 weeks (±7 days) until radiographic documentation of PD, death, start of Part B, or study completion, except when not feasible in the opinion of the investigator due to the patient's clinical status.

During the pre-treatment period of Part B, radiographic assessment should be completed as part of the baseline assessment of Part B within 28 days prior to first treatment of Part B.

For Part B, tumor assessments are to be performed every 6 weeks (±7 days) from first treatment of Part B for the first year, and every 9 weeks (±7 days) thereafter, even if treatment is delayed, until there is radiographic documentation of PD. Further radiographic assessments after treatment discontinuation will not be required for patients who discontinue for reasons other than radiographically documented PD.

8.1.2. Pre-treatment Period of Part B

The pre-treatment period of Part B begins the day after the decision is made that the patient will no longer continue study treatment of Part A. Patients who meet initiation criteria of Part B can start administration of study treatment of Part B (see Section 9.B.4.1.1). Patients who do not meet initiation criteria of Part B within 12 weeks from decision of study treatment discontinuation of Part A should be discontinued from the study. Patients who will start next treatment other than Part B treatment or decide not to move to Part B must be followed for 30 days (±7 days) after the decision is made that the patient will discontinue from the study.

8.1.3. Postdiscontinuation Follow-Up

Adverse event information will be collected until at least 30 days after the decision is made that the patient will not move to Part B (eg, the patient does not meet initiation criteria of Part B [see Section 9.B.4.1.1] within 12 weeks from decision of study treatment discontinuation of Part A) or no longer continue study treatment of Part B. After the 30-day short-term safety follow-up visit, only new and ongoing SAEs deemed related to study treatment will be collected.

Following the short term safety follow-up period, information regarding further anticancer treatment and survival status will be collected every 12 weeks (±14 days). Follow-up will

continue as long as the patient is alive, or until sufficient OS-related information is collected (as defined in Section 8.1.4).

8.1.4. Study Completion and End of Trial

This study will be considered complete (ie, the scientific evaluation will be complete [study completion]) when the primary endpoint analysis (6 months after observing 111 PFS events) has been performed and evaluated and sufficient OS-related information is collected for analysis, as determined by the Sponsor. The OS analysis may require a separate database lock after the one for the primary endpoint analysis. Investigators will continue to follow the Study Schedule (see Attachment 1, as applicable) for all patients until notified by Lilly that study completion has occurred.

Blinding of Part A will be kept until DBL for the primary endpoint analysis is achieved, even if patients move to Part B or discontinue from the study. Upon DBL for the primary endpoint analysis, investigators and patients may be unblinded to study treatment assignment.

"End of trial" refers to the date of the last visit or last scheduled procedure for the last patient. The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up (Figure JVCW.8.3).
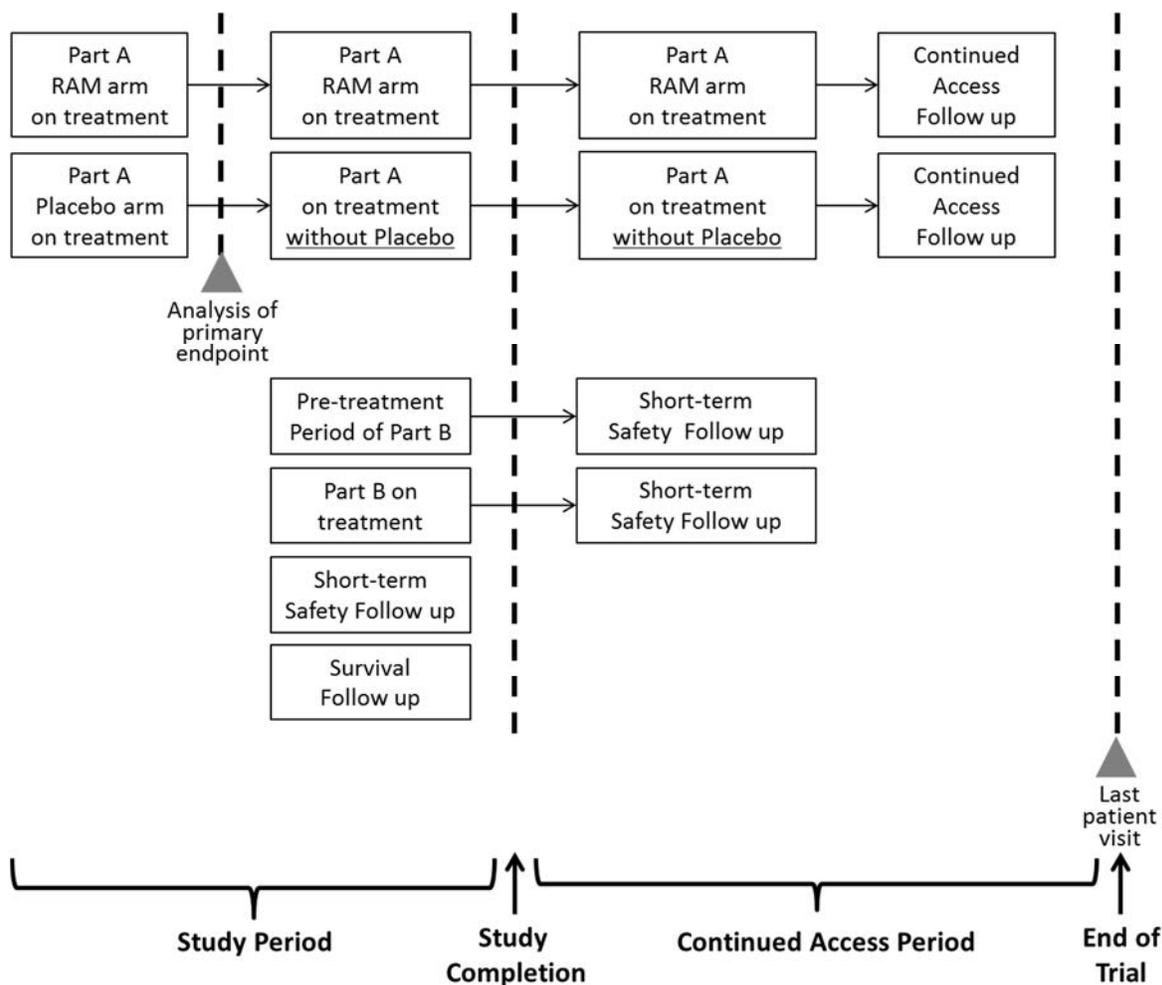
Abbreviation: RAM = ramucirumab.

Figure JVCW.8.3.   Illustration of study completion and end of trial.

8.1.5. Continued Access Period

Continued access will start after study completion (ie, after the primary endpoint analysis has been performed and sufficient OS-related information is collected for analysis). Patients receiving study treatment of Part A and experiencing ongoing clinical benefit and no undue risks may continue to receive study treatment of Part A in the continued access period until one of the criteria for discontinuation is met (Section 7.3). After DBL for the primary endpoint analysis, placebo will no longer be administered. Lilly will notify investigators when the continued access period begins.

- Patients who are in Part A treatment when the continued access period begins will continue the study treatment of Part A until any other discontinuation criteria are met.

- Patients who are in Part B treatment when the continued access period begins will discontinue the study treatment, and the short-term safety follow-up will be done prior to starting subsequent anticancer treatment.
- Patients who are in pre-treatment of Part B or in the short-term safety follow-up period when the continued access period begins will continue in short-term safety follow-up until the short-term safety follow-up visit is completed.

During the continued access period, drug administration information, reasons for discontinuation, and all AEs and SAEs will be reported on the case report form (eCRF; see Attachment 2). Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.2.1.2). 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. Blood samples for PK and immunogenicity analyses will be collected in the event of an infusion-related reaction (IRR; as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event).

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.

8.1.6. Independent Radiography Review Committee

Since 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, copies of all scans will be collected throughout the study and stored centrally by a coordinating vendor designated by Lilly.

8.2. Discussion of Design and Control

A randomized, double-blind, placebo-controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study treatment and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study treatment and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses.

Investigational treatment administration in this study is double-blind, meaning that patients, investigational sites, and the sponsor study team do not have access to treatment assignments for any patients. Blinding of Part A will be kept until DBL for the primary endpoint analysis is achieved, even if patients move to Part B or discontinue from the study. After DBL for the primary endpoint analysis, placebo will no longer be administered. This design feature minimizes potential bias and imbalance due to knowledge of patient's treatment during evaluation of study endpoints, at the patient level or aggregated across patients. Emergency

unblinding can only occur for medical safety reasons where the identity of the study treatment is integral to the treatment of the AE (see Section 9.A.5.1 and Section 9.B.5.1).

9. Treatment

9.A. Treatment of Part A

9.A.1. Treatments Administered

Upon completion of screening procedures, eligible patients with metastatic gastric or GEJ adenocarcinoma will be randomly assigned on a 1:1 basis to receive either ramucirumab (8 mg/kg) in combination with S-1 and oxaliplatin or placebo in combination with S-1 and oxaliplatin (Part A) followed by treatment with ramucirumab plus paclitaxel (Part B).

Principally, a cycle is defined as an interval of 21 days in Part A (Note: A delay due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 days and will not be counted as a protocol deviation. Additionally, in a circumstance where Lilly confirms that a delay will be permitted over 3 days, such as a New Year's holiday or similar, this instance will not be counted as a protocol deviation.). In Part A, a cycle will begin at the Day 1 administration of any component of chemotherapy treatment. In case of discontinuation of S-1 and oxaliplatin, a new cycle will be started on Day 22 (Day 1 of the new cycle) with the administration of ramucirumab/placebo monotherapy.

For Part A, patients will receive ramucirumab in combination with S-1 and oxaliplatin (Arm A) or placebo in combination with S-1 and oxaliplatin (Arm B) on Day 1 of each cycle (21 days [3 weeks]) (Table JVCW.9.A.1). Oxaliplatin will be administered after ramucirumab treatment. S-1 will be started on the evening of Day 1 and the final dose of S-1 for that cycle will be administered on the morning of Day 15. Ramucirumab (8 mg/kg) or placebo will be administered as an approximately 1-hour I.V. infusion followed by an approximately 1-hour observation period for initial the 2 administrations. In the first cycle, patients will receive oxaliplatin after the observation period. If there is no evidence of an IRR during the initial 2 administrations of ramucirumab/placebo, then no observation period is required for subsequent treatment cycles. In the event that an IRR occurs thereafter, the approximately 1-hour observation should be reinstituted. S-1 should be taken after a meal. Premedication is required prior to infusion of ramucirumab/placebo. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at investigator discretion. See also Section 9.A.4.1.4.2.1 for premedication guidelines for Grade 1 or Grade 2 IRRs. All premedication administered must be adequately documented in the electronic case report form (eCRF). Figure JVCW.9.A.1 illustrates and Table JVCW.9.A.1 presents the treatment regimens/dosing schedule for Part A.

First-Line Part (Part A)

Ramucirumab or Placebo	Observation Period	Oxaliplatin
1 hour	1 hour	2 hours

Note: S-1 will be started on the evening of Day 1, in which case the final dose of S-1 for that cycle will be administered on the morning of Day 15.

Figure JVCW.9.A.1.   Illustration of treatment regimen/dosing schedule for Part A.

Table JVCW.9.A.1.   Treatment Regimens/Dosing Schedule

	Drug[a]	Dose	Time for Administration
Part A (21-day Cycle)			
ARM A	S-1[b]	80-120 mg/day	Administered po, twice daily on Day 1-Day 14
	Ramucirumab[c,d]	8 mg/kg I.V.	Administered over approximately 60 min on Day 1 and Day 8
	Oxaliplatin[e]	100 mg/m^2 I.V.	Administered over 120 min on Day 1
ARM B	S-1[b]	80-120 mg/day	Administered po, twice daily on Day 1-Day 14
	Placebo[c,d]	Volume equivalent to 8 mg/kg I.V.	Administered over approximately 60 min on Day 1 and Day 8
	Oxaliplatin[e]	100 mg/m^2 I.V.	Administered over 120 min on Day 1

Abbreviations: I.V. = intravenously; min = minutes; po = orally.

Note: All treatments are administered in the order shown in the table.

[a] Ramucirumab/placebo, S-1, and oxaliplatin will be administered until disease progression or other withdrawal criteria are met.

[b] S-1 should be taken after a meal. Total daily dose of S-1 administered will be 80-120 mg/day. S-1 will be started on the evening of Day 1 and the final dose of S-1 for that cycle will be administered on the morning of Day 15.

[c] Premedication with an intravenous histamine H1 antagonist, such as diphenhydramine hydrochloride (or equivalent), is required prior to infusion of ramucirumab/placebo. See also Section 9.A.4.1.4.2.1 for premedication guidelines for Grade 1 or 2 infusion-related reactions.

[d] A 1-hour observation period following the ramucirumab/placebo infusion is mandatory for the first 2 administrations. If there is no evidence of an infusion-related reaction to ramucirumab/placebo after the administration of the first 2 administrations, then no observation period is required for subsequent administrations. Administration of antiemetics can occur during this same time period (see Section 9.A.6.1.2).

[e] If the total dose of oxaliplatin exceeds 600 mg/m^2, administration of oxaliplatin can be skipped at the discretion of investigators to ensure patients' safety.

Dose reductions of investigational product and/or chemotherapy will be made in the event of specific treatment-related AEs, as described in Section 9.A.4.1. Supportive care guidelines are detailed in Section 9.A.6.1.

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 patient/site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of IP 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 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.

For Part A, ramucirumab/placebo is considered as the investigational medicinal product and S-1 and oxaliplatin as the background standard chemotherapy for first-line therapy in this disease type.

All products will be administered according to the instructions below.

9.A.1.1. Premedication

9.A.1.1.1. Premedication Prior to Infusion of Ramucirumab or Placebo

Premedication with an I.V. histamine H1 antagonist, such as diphenhydramine hydrochloride (or equivalent), is required prior to infusion of ramucirumab/placebo. Additional premedication may be provided at investigator discretion. See also Section 9.A.4.1.4.2.1 for premedication guidelines for Grade 1 or 2 IRRs. All premedication administered must be adequately documented in the eCRF.

9.A.1.2. Preparation and Administration of Ramucirumab/Placebo

Aseptic technique is to be used when preparing and handling ramucirumab/placebo for infusion. Patients will receive ramucirumab/placebo by I.V. infusion over approximately 60 minutes at 8 mg/kg on Day 1 and Day 8 every 21 days (Part A) in the absence of disease progression or until other withdrawal criteria are met. The first dose of ramucirumab/placebo is dependent upon the patient's baseline body weight in kilograms. Patients should be weighed at the beginning of each cycle (defined in the study schedule; Attachment 1). If there is a $\geq 10\%$ change (increase or decrease) in body weight from the last dose calculation, then the dose of ramucirumab/placebo **must** be recalculated. 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.

Ramucirumab is compatible with common infusion containers. Details regarding infusion sets that are compatible for ramucirumab infusion can be found in the JVCW Additional Pharmacy/Dispensing Instructions and the IB.

Based on the calculated volume of ramucirumab/placebo, add (or remove from pre-filled [with 0.9% normal saline] I.V. infusion container) a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to make the total volume 250 mL. For dose volumes greater than 250 mL, the addition of sterile normal saline is not required. Do not use dextrose-containing solutions. The container should be gently inverted to ensure adequate mixing. The infusion should be delivered via infusion pump in approximately 60 minutes. The infusion rate should not exceed 25 mg/minute. Infusions of duration longer than 60 minutes are permitted in specific circumstances (ie, for larger patients in order to maintain an infusion rate that does not exceed 25 mg/minute, or in the setting of prior ramucirumab IRR); the infusion duration must always be accurately recorded. The infusion set must be flushed post infusion with sterile 0.9% normal saline equal to or greater than infusion set hold-up volume to ensure delivery of the calculated dose.

See Section 9.A.1.1.1 for premedication guidelines prior to infusion of ramucirumab/placebo.

CAUTION: IRRs may occur during or following ramucirumab administration (see Attachment 8 for a definition of Grade 3 and 4 IRRs). During the administration of ramucirumab/placebo, patients should be in an area with resuscitation equipment and treatments necessary for advanced life support and cardiopulmonary resuscitation, such as bronchodilators, vasopressor agents (eg, epinephrine), oxygen, glucocorticoids, antihistamines, and I.V. fluids. A 1-hour observation period is required after the administration of the initial 2 administrations of ramucirumab/placebo in Part A. If there is no evidence of an IRR during the initial 2 administrations of ramucirumab/placebo, then no observation period is required for subsequent administrations. In the event that an IRR occurs thereafter, the 1-hour observation should be reinstituted.

9.A.1.3. Administration of S-1

S-1 will be administered orally twice daily (from the evening of Day 1 to the morning of Day 15, or from the morning of Day 1 to the evening of Day 14) at the standard doses, as defined by the initial dose for adults according to body surface area. S-1 is administered twice daily, after breakfast and after the evening meal, for 14 consecutive days, followed by a 7-day rest (Table JVCW.9.A.2). S-1 will be started on the evening of Day 1 and the final dose of S-1 for that cycle will be administered on the morning of Day 15.

Table JVCW.9.A.2.   **S-1 Dosing**

	S-1 Dosing		
Body surface area (m^2)	**<1.25**	**1.25 - <1.5**	**≥1.5**
Level 0 (Initial Dose)	80 mg/day	100 mg/day	120 mg/day
Level -1	60 mg/day	80 mg/day	100 mg/day
Level -2	40 mg/day	60 mg/day	80 mg/day

Note that the same formula is to be used for body surface area during the treatment period of Part A.

9.A.1.4. Preparation and Administration of Oxaliplatin

Investigators should consult the manufacturer's instructions for oxaliplatin for complete prescribing information and follow institutional procedures for the administration of oxaliplatin.

Patients will receive oxaliplatin by I.V. infusion over approximately 120 minutes at 100 mg/m^2 on Day 1 of every 21-day cycle.

According to the guidance for dose modification (Section 9.A.4.1.5), the oxaliplatin dose may be reduced up to Level -2 (Table JVCW.9.A.3). Oxaliplatin will be administered after the completion of the ramucirumab/placebo infusion or after a 1-hour observation period following the first 2 administrations of ramucirumab/placebo.

If the total dose of oxaliplatin exceeds 600 mg/m^2, administration of oxaliplatin can be skipped at the discretion of the investigator to ensure patients' safety.

Table JVCW.9.A.3.   **Oxaliplatin Dosing**

Dose Level	Oxaliplatin Dosing
Level 0 (Initial Dose)	100 mg/m^2 / 3 weeks
Level -1	75 mg/m^2 / 3 weeks
Level -2	50 mg/m^2 / 3 weeks

Note that the same formula is to be used for body surface area during treatment period of Part A.

9.A.2. Materials and Supplies

Ramucirumab and placebo will be provided by Lilly. S-1 and oxaliplatin will be obtained locally. Clinical trial materials provided by Lilly will be labeled according to the country's regulatory requirements.

9.A.2.1. Ramucirumab

Ramucirumab is a sterile, preservative-free solution for infusion of ramucirumab formulated in an aqueous solution at a concentration of 10 mg/mL (500 mg/50-mL vial). The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80, pH 6.0.

All excipients used for the manufacture of ramucirumab are of pharmacopeial grade. No animal-derived components are used in the manufacture of ramucirumab excipients.

Refer to the current version of the ramucirumab IB for safe handling and administration details.

9.A.2.2. Placebo

Placebo product is a sterile, preservative-free solution for infusion formulated in histidine buffer. The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80, pH 6.0.

All excipients used for the manufacture of placebo are of pharmacopeial grade. No animal-derived components are used in the manufacture of placebo excipients.

9.A.2.3. Chemotherapy Agents

Commercial preparations of S-1 and oxaliplatin will be used in this study, and will be packaged, labeled, and stored according to manufacturer standards and according to the country's regulatory requirements, if supplied by the sponsor.

9.A.3. Method of Assignment to Treatment

Upon completion of all screening evaluations to confirm a patient's eligibility, the site will register the patient via the interactive web response system (IWRS), which is accessible 24 hours a day. The IWRS registration consists of assigning the patient a unique study identification number and randomizing the patient to 1 of the 2 treatment arms on a 1:1 basis.

The IWRS will assign patients to treatment arms according to a stratified method of randomization (ie, independent randomization within each of the following prognostic factors):

- ECOG PS (0 vs. 1)
- region (Japan vs. Other [South Korea/Taiwan])
- disease measurability (measurable vs. nonmeasurable)

Once the patient is registered through the IWRS, he/she is considered to be enrolled in the study.

9.A.4. Selection and Timing of Doses

A cycle is defined as an interval of 21 days in Part A. (Note: A delay due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 days and not be counted as a protocol deviation. Additionally, in a circumstance where Lilly confirms that a delay will be permitted over 3 days, such as a New Year's holiday or similar, this instance will not be counted as a protocol deviation.). A cycle will begin at the Day 1 administration of any component of chemotherapy treatment. Ramucirumab/placebo cannot be administered on a

consecutive third week even though the planned Day 1 of a new cycle is delayed due to delay of chemotherapy treatment. In the event of discontinuation of S-1 and oxaliplatin, a new cycle will be started on Day 22 (Day 1 of the new cycle) with the administration of ramucirumab monotherapy. If a patient discontinues any component of study treatment, Day 1 will be based on the administration of the remaining study component(s).

Patients may continue to receive ramucirumab/placebo, S-1, and oxaliplatin in Part A until 1 or more of the specified reasons for discontinuation are met (as described in Section 7.3).

9.A.4.1. Special Treatment Considerations

9.A.4.1.1. Discontinuation from Part A

In the following circumstances; if patients are in Part A, patients will be discontinued from study treatment of Part A and move to Part B as long as they meet the criteria to initiate treatment of Part B within 12 weeks after decision of study treatment discontinuation of Part A.

- Any study treatment-related event that is deemed life-threatening if the event is considered possibly related to any components of study therapy.

- Any unacceptable AE/toxicity (eg, a persistent moderate toxicity that is intolerable to the patient)

- Evidence of progressive disease per RECIST v1.1 criteria. In case of treatment discontinuation for any reason other than radiographically confirmed PD, radiographic tumor assessments will continue according to the protocol schedule, except when not feasible in the opinion of the investigator due to patient's clinical status.

    o **Note:** Discontinuation from all or any study treatment for reasons other than radiographically confirmed PD should be based on strong clinical justification. If discontinuation is required (eg, due to toxicity), investigators should consider an initial discontinuation of one study agent, followed by the additional agent(s) if required.

- The investigator decides that the patient should be discontinued from study treatment in Part A.

- The patient requests to be withdrawn from study treatment in Part A.

If 1 (or 2) therapeutic agent(s) is permanently discontinued, then treatment with the other study agent(s) should continue and the patient should remain on study with full adherence to all protocol-related requirements as clinically appropriate.

Study blinding will continue through disease progression/subsequent lines of treatment until DBL for the primary endpoint analysis is achieved (see Section 8.1.4). Lilly will not supply ramucirumab or any other study drugs outside of the study treatment schedule as defined in Section 8.1.

9.A.4.1.2. Discontinuation of Ramucirumab/Placebo (Part A)

9.A.4.1.2.1. Permanent Discontinuation of Ramucirumab/Placebo

Patients will be permanently discontinued from ramucirumab/placebo for any of the following reasons:

- **Arterial thromboembolic event (ATE):** Any Grade 3-4 ATE

- **Severe bleeding:** Grade 3-4 bleeding due to any reason;

- **Hypertension** that cannot be medically controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy;

- **Infusion-related reaction:** Any Grade 3-4 IRR that is clearly attributed to ramucirumab/placebo;

- **Gastrointestinal perforation or fistulae**: Any grade GI perforation or fistulae;

- **New occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis**;

- **Reversible posterior leukoencephalopathy syndrome (RPLS)**;

- **Urine protein**: level of $\geq$3 g/24 hours or in the setting of nephrotic syndrome.

In the event that patients meet these criteria and are discontinued from ramucirumab/placebo permanently in Part A, patients will not be able to receive ramucirumab in Part B. In this case, patients can continue Part A treatment with S-1 and oxaliplatin and can start Part B treatment with paclitaxel only.

9.A.4.1.2.2. Discontinuation of Ramucirumab/Placebo in Part A

Patients will be discontinued from ramucirumab/placebo within Part A for any of the following reasons. In the event that patients meet these criteria and are discontinued from ramucirumab/placebo in Part A, patients will still be able to receive ramucirumab in Part B:

- **Dose modifications:** >2 dose reductions

- **Venous thromboembolic event (VTE):** A Grade 3-4 VTE occurs that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy

- **Impaired wound healing:** Discontinue ramucirumab if wound is not fully healed within 42 days after withholding from the next planned dose of ramucirumab/placebo;

- **Any Grade 4 (life-threatening) nonhematologic toxicity** considered by the investigator to be possibly, probably, or definitely related to ramucirumab/placebo;

- **Any pulmonary embolism (PE)/deep vein thrombosis (DVT)** occurring or intensifying during anticoagulant therapy;

- **Congestive heart failure (CHF):** Any Grade 3-4 events that are consistent with CHF.

Patients who are discontinued from ramucirumab/placebo will continue to be in the study, and should continue to receive the other components of study treatment (if appropriate), in accordance with the protocol.

9.A.4.1.3. Discontinuation of S-1 and/or Oxaliplatin in Part A

Patients will be discontinued from S-1 and/or oxaliplatin in Part A for the following reason:

- **Dose modifications:** >2 dose reductions.

Patients who are permanently discontinued from S-1 or oxaliplatin in Part A will continue to be in the study, and should continue to receive the other components of study treatment (if appropriate), in accordance with this protocol (eg, if a patient discontinues S-1 in Part A, the patient can continue oxaliplatin and ramucirumab/placebo).

The criteria for dose modifications due to AEs related to S-1 and oxaliplatin (Part A) are described in Section 9.A.4.1.5.

9.A.4.1.4. Recommended Dose Modification Guidelines for Ramucirumab/Placebo (Part A)

The following are general principles for dose modifications of ramucirumab/placebo in Part A:

- Treatment for the first cycle should only commence if all the inclusion and exclusion criteria are met and the patient has been randomized to an arm of treatment via IWRS. For subsequent cycles, dose delay/modification is permitted as described in sections specific for ramucirumab/placebo (Section 9.A.4.1.4), and S-1 and oxaliplatin (Section 9.A.4.1.5). All study treatment will be discontinued in case of disease progression (Section 9.A.4.1.1).

- Ramucirumab/placebo dose modifications are not required for hematologic laboratory abnormalities unless associated with clinical symptoms. As an initial step, the dose of chemotherapy should be reduced first before any dose reductions for ramucirumab/placebo are considered.

- Ramucirumab/placebo dose modifications are permanent; no dose escalations are allowed after dose reductions in Part A.

- Control hypertension prior to initiating treatment with ramucirumab/placebo. Temporarily suspend ramucirumab/placebo for severe hypertension until medically controlled.

- Ensure any wound is fully healed prior to commencing or continuing ramucirumab/placebo.

- Ramucirumab/placebo therapy should continue as scheduled if there is a delay or discontinuation of S-1 and/or oxaliplatin. When the subsequent cycle of chemotherapy is initiated, administration of ramucirumab/placebo and chemotherapy will be resynchronized according to the study design described in this protocol (ie, the cycle will begin at Day 1 for both ramucirumab and chemotherapy). Doses of ramucirumab/placebo omitted are not replaced or restored; instead, the patient should resume the planned treatment cycles.

- In the case of ramucirumab/placebo-related toxicity, ramucirumab/placebo will be delayed for 1 week and administered on Day 8 of the treatment cycle provided that ramucirumab/placebo-related toxicities have resolved to Grade <2 or baseline. If toxicities have not resolved on Day 8, omit ramucirumab/placebo for that cycle.

- If a toxicity related to ramucirumab/placebo does not resolve in the same treatment cycle, the administration of ramucirumab/placebo can be delayed up to 42 days from the planned dose of ramucirumab/placebo. If the toxicity does not resolve within 42 days, ramucirumab/placebo will be discontinued unless it is determined by the treating investigator that the patient might benefit from continuation of ramucirumab/placebo and there are no additional safety risks involved. These situations will need to be approved by the Lilly CRP or CRS in consultation with the treating investigator. Circumstances that may lead to withholding ramucirumab/placebo include:

  o Unscheduled surgery or any other invasive procedure(s) that may be associated with increased bleeding and continuation of ramucirumab/placebo is contraindicated;
  o A period of discontinuation required for wound healing such that continuation of ramucirumab/placebo could delay the process of healing;
  o Hypertension not controlled (see Section 9.A.4.1.4.2.2) with existing medications and requiring additional clinical evaluation;
  o A reversible non-life threatening toxicity that, in the opinion of the investigator, is likely to resolve after a brief period of omission of study drug, and there are no added concerns in continuing ramucirumab;
  o An interval period to allow resolution of an AE or an abnormal laboratory parameter to a level that is considered safe to allow continuation of ramucirumab/placebo (eg, proteinuria).

- If there is a delay or modification in administration of ramucirumab/placebo due to toxicity, treatment with other study agent(s) should continue as scheduled. If clinically appropriate, the investigator can delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents.

9.A.4.1.4.1. Recommended Dose Modification Guidelines for Ramucirumab/Placebo for Specific Adverse Events (Part A)

Table JVCW.9.A.4 provides dose modification guidelines for ramucirumab/placebo for specific AEs related to administration of ramucirumab/placebo in Part A. Refer to Section 9.A.4.1.2 for criteria for discontinuation of ramucirumab/placebo.

Table JVCW.9.A.4.   Recommended Dose Modification Guidelines for Ramucirumab/Placebo for Specific Adverse Events – Part A

Toxicity related to administration of ramucirumab/placebo			Gr	Dose Adjustment for Ramucirumab/Placebo
Reversible, non-life-threatening toxicity (eg, fatigue/anorexia/fever/laboratory abnormalities[a]). For hypertension, see below.	First instance		3/4	8 mg/kg (full dose) on recovery to Grade ≤1
	Second instance		3/4	6 mg/kg (first dose reduction) for next dose on recovery to Grade ≤1
	Third instance		3/4	5 mg/kg (second dose reduction) for next dose on recovery to Grade ≤1
	Subsequent instance		3/4	Discontinue (if a third dose reduction is required) (see Section 9.A.4.1.2)
Infusion-related reactions			1/2	If clinically indicated, stop the infusion temporarily and then reduce the infusion rate of ramucirumab/placebo by 50%. See Section 9.A.4.1.4.2.1.
			3/4	Discontinue (see Section 9.A.4.1.2)
Hypertension	**Hypertension controlled with medications**		1	8 mg/kg (full dose) without interruption
	Hypertension (non-life threatening and symptomatic)	Resolution to Grade <2 within 3 weeks	2/3	Delay ramucirumab/placebo administration. Administer 8 mg/kg (full dose) once hypertension is controlled with medications and is Grade <2 within 3 weeks.
		Resolution to Grade <2 within 3 to 6 weeks	2/3	Delay ramucirumab/placebo administration. Administer ramucirumab/placebo at 6 mg/kg if hypertension is Grade <2 by the fourth week. Administer ramucirumab/placebo at 5 mg/kg if hypertension is Grade <2 by the sixth week. Discontinue ramucirumab/placebo if blood pressure does not improve to Grade <2 by the sixth week (42 days from the next planned dose of ramucirumab/placebo). See Section 9.A.4.1.4.2.2.
	Uncontrolled hypertension, hypertensive crisis, hypertensive encephalopathy		4	Discontinue (see Section 9.A.4.1.4.2.2).
Congestive heart failure			3/4	Discontinue (see Section 9.A.4.1.2)

Dose Modification Guidelines for Ramucirumab/Placebo for Specific Adverse Events – Part A

Toxicity related to administration of ramucirumab/placebo			Gr	Dose Adjustment for Ramucirumab/Placebo
Proteinuria **Note:** The protein algorithm is provided in Attachment 10.	**Proteinuria (dipstick <2+)**			Administer baseline or full previous dose of ramucirumab/placebo without interruption. See Section 9.A.4.1.4.2.5.
	Proteinuria (dipstick 2+)			Administer full previous dose of ramucirumab/placebo without interruption. Perform a 24-hour urine collection within 3 days prior to next ramucirumab/placebo dose administration.[c] If the 24-hour collection shows proteinuria <2 g/24 hours, administer unchanged dose of ramucirumab/placebo. If ≥2 g/24 hours, then follow dose adjustment based on 24-hour collection (below). See Section 9.A.4.1.4.2.5.
	Proteinuria (dipstick >2+)			Delay ramucirumab/placebo administration. Perform a 24-hour urine collection within 3 days prior to ramucirumab/placebo administration.[c] If the 24-hour collection shows proteinuria <2 g, administer unchanged dose of ramucirumab/placebo. If ≥2 g, then follow dose adjustment based on 24-hour collection (below). See Section 9.A.4.1.4.2.5.
	Proteinuria based on 24-hour urine collection ≥2 g/24 hours[b,c]	First instance		6 mg/kg once urinary protein returns to <2 g/24 hours
		Second instance		5 mg/kg once urinary protein returns to <2 g/24 hours
		Third instance		Discontinue (if a third dose reduction is required) (see Section 9.A.4.1.2).
	Proteinuria based on 24-hour urine collection >3 g/24 hours[b,c] or in the setting of nephrotic syndrome			Discontinue (see Section 9.A.4.1.2).
Arterial thromboembolic events, venous thromboembolic events, or bleeding			3/4	Discontinue (see Section 9.A.4.1.2).
Gastrointestinal perforation or fistulae			Any	Discontinue (see Section 9.A.4.1.2).
RPLS				Discontinue (see Section 9.A.4.1.2).
Liver injury/liver failure			Any	Discontinue (see Section 9.A.4.1.2).

a   Dose modifications are not required for hematologic laboratory abnormalities unless associated with clinical symptoms. As an initial step, the dose of chemotherapy should be reduced first before any dose reductions for ramucirumab/placebo are considered.

b   A dipstick test for proteinuria should be performed prior to each infusion of ramucirumab/placebo. If both dipstick and 24-hour tests are performed, the results of 24-hour collection should be used for clinical decision-making.

c   Although it is recommended to perform a 24-hour urine collection, urine protein/creatinine ratio measured in urine sample can be used to check the urine protein level if implementation of 24-hour urine collection is difficult. In the event that the urine protein/creatinine ratio is 1, 24-hour urine collection will be 1 g/24 hours.

9.A.4.1.4.2. Treatment Guidelines for Specific Adverse Events Related to Ramucirumab/Placebo (Part A)

Adverse events of special interest which may or may not be associated with ramucirumab therapy may include IRRs, hypertension, ATEs, VTEs, bleeding (hemorrhagic) events, GI perforation, proteinuria, CHF, surgery and impaired wound healing, liver injury/liver failure, and RPLS.

9.A.4.1.4.2.1. Infusion-Related Reactions

Any treatment-related IRRs are defined according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 4.03 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. Those IRRs described above should be graded as shown in Attachment 8.

Consistent with usual medical practice, the patient should be clinically monitored and selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below. The Lilly CRP, CRS, or designee should be contacted immediately if questions arise concerning the grade of the reaction.

The following are treatment guidelines for IRRs.

Clinical and laboratory monitoring:

- Time (24-hour clock)

- Body temperature in Celsius

- Arterial pulse rate in beats per minute

- Respiratory rate per minute

- Systolic blood pressure in mm Hg

- Diastolic blood pressure in mm Hg

- Other investigations as clinically necessary (eg, oxygen saturation, chest x-ray, electrocardiogram [ECG])

- All attempts should be made to obtain a blood sample for anti-ramucirumab antibody analysis as close to the onset of the event as possible, at the resolution of the event, and approximately 30 days following the event. Additional samples may be assessed for levels of ramucirumab and other tests to provide information on the nature of the IRR.

Grade 1 IRR

- Slow the infusion rate by 50%.

- Monitor the patient for worsening of condition.

- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion.

Grade 2 IRR

- Stop the infusion.

- Administer I.V. diphenhydramine hydrochloride 50 mg (or equivalent), acetaminophen 650 mg orally for fever, and oxygen.

- Resume the infusion at 50% of the prior rate once the IRR has resolved or decreased to Grade 1; the infusion duration should not exceed 2 hours.

- Monitor for worsening of condition.

- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion.

For a second Grade 1 or 2 IRR, administer I.V. dexamethasone 8-20 mg (or equivalent); for subsequent infusions, premedicate with I.V. diphenhydramine hydrochloride 50 mg (or equivalent), acetaminophen 650 mg orally, and I.V. dexamethasone 8-20 mg (or equivalent).

Grade 3 or Grade 4 IRR

- Stop the infusion and disconnect the infusion tubing from the patient.

- Administer I.V. diphenhydramine hydrochloride (or equivalent, per institutional guidelines), I.V. dexamethasone (or equivalent, per institutional guidelines), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.

- Give epinephrine or bronchodilators as indicated.

- Hospital admission for observation may be indicated.

- Patients who have a Grade 3 or 4 IRR will not receive further ramucirumab/placebo treatment, but will continue to be followed on the protocol.

9.A.4.1.4.2.2. Hypertension

The following are general treatment guidelines for hypertension (an expected AE in patients receiving ramucirumab) during the study. Uncontrolled hypertension is defined as Grade >2 in NCI-CTCAE v. 4.03 (the patient continues to clinically experience raised blood pressure [systolic ≥160 mm Hg and/or diastolic ≥100 mm Hg] despite medications). Every attempt should be made to control the blood pressure to systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg prior to starting treatment with ramucirumab/placebo. Investigators have the discretion to consider the clinical circumstances of individual patients, especially involving borderline hypertension, and to administer unchanged doses of ramucirumab/placebo for blood pressure up to systolic blood pressure 150 mm Hg and diastolic blood pressure 90 mm Hg, if clinically appropriate. Routine clinical and laboratory monitoring is highly recommended in patients who develop de novo hypertension or experience a deterioration in previous hypertension. Control hypertension prior to initiating treatment with ramucirumab/placebo. Monitor blood pressure prior to every administration of ramucirumab/placebo or more frequently as indicated during treatment. For dose modifications guidelines, refer to Table JVCW.9.A.4.

Grade 1 hypertension

- Continue ramucirumab/placebo therapy at baseline or previous dose. Initiate or continue antihypertensive therapy if clinically indicated.

Grade 2 or Grade 3 hypertension

- If the hypertension is not associated with symptoms, continue ramucirumab/placebo therapy and initiate or continue antihypertensive therapy.

- If the hypertension is associated with symptoms, hold ramucirumab/placebo therapy and initiate or continue antihypertensive therapy until symptoms resolve to Grade <2 (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg)

- If ramucirumab/placebo administration is interrupted due to hypertension or related symptoms,

  o review blood pressure once a week for 3 weeks, and if Grade <2 administer previous dose of ramucirumab/placebo.

  o if blood pressure improves to Grade <2 by the fourth week, reduce ramucirumab/placebo dose to 6 mg/kg on Day 1 and Day 8.

  o if blood pressure improves to Grade <2 by the sixth week, reduce ramucirumab/placebo dose to 5 mg/kg on Day 1 and Day 8.

o if blood pressure does not improve to Grade <2 by the sixth week (42 days from the next planned dose of ramucirumab/placebo), discontinue ramucirumab/placebo.

Grade 4 or refractory hypertension

- Patients with Grade 4 hypertension (life-threatening consequences; for example, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis; or urgent intervention indicated) or patients whose hypertension is poorly controlled (≥160 mm Hg systolic or ≥100 mm Hg diastolic for >6 weeks [>42 days from the next planned dose of ramucirumab/placebo]) despite appropriate oral medication (eg, 2 or more oral agents at maximum tolerated dose) will be discontinued from ramucirumab/placebo.

9.A.4.1.4.2.3. Thromboembolic Events

Investigators should perform all testing required to fully characterize ATEs or VTEs. The incidence and type of thrombotic/vascular events will be collected and reported.

Ramucirumab/placebo therapy should be discontinued in the event of any Grade 3 or 4 ATE or VTE that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy. At the investigator's discretion, ramucirumab/placebo therapy may be continued in the setting of an incidentally diagnosed, asymptomatic DVT or PE or following a symptomatic DVT or PE when symptoms have resolved with the institution of anticoagulation therapy.

Ramucirumab/placebo should also be discontinued in the setting of a DVT or PE that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

9.A.4.1.4.2.4. Bleeding (Hemorrhagic) Events

Serious hemorrhagic AEs have been reported from clinical studies investigating ramucirumab. Hemorrhagic complications are associated with some malignancies (ie, 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 precludes any definitive association between bleeding and ramucirumab. Ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential and is detailed in the inclusion/exclusion criteria.

Discontinue ramucirumab/placebo in the event of a Grade 3 or 4 bleeding (hemorrhagic) event.

9.A.4.1.4.2.5. Proteinuria

If, while on ramucirumab/placebo therapy, a patient has proteinuria ≥2+ per a dipstick or routine urinalysis test, a 24-hour urine collection will be conducted. If the protein level is <2 g/24 hours, the patient will continue on ramucirumab/placebo therapy at the same dose without interruption.

If the dipstick is 2+, administer full previous dose of ramucirumab/placebo without interruption. Perform a 24-hour urine collection within 3 days prior to next ramucirumab/placebo dose administration. If the 24-hour collection shows proteinuria <2 g/24 hours, administer unchanged dose of ramucirumab/placebo. If the protein level is ≥2 g/24 hours, delay ramucirumab/placebo administration and perform a 24-hour urine collection prior to the next planned dose of ramucirumab/placebo. Ramucirumab/placebo treatment will resume at a reduced dose level (6 mg/kg) once the protein level returns to <2 g/24 hours. A second dose reduction of ramucirumab/placebo to 5 mg/kg is permitted in case of a second instance of proteinuria ≥2 g/24 hours. The patient will be discontinued from ramucirumab/placebo treatment if the protein level is >3 g/24 hours, if there is a third occurrence of proteinuria ≥2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 42 days of interruption from the next planned dose of ramucirumab/placebo.

For dose modification guidelines, refer to Table JVCW.9.A.4.

9.A.4.1.4.2.6. 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.

Patients with a history of GI perforation within 6 months prior to randomization are excluded from participation (see Section 7.2). Ramucirumab/placebo should be permanently discontinued in the event of a GI perforation.

9.A.4.1.4.2.7. Congestive Heart Failure
In patients who received ramucirumab in combination with mitoxantrone (Study JVBS, in patients with androgen-independent prostate cancer) or following prior anthracycline therapy (Study JVBX, in patients with locally advanced or metastatic breast cancer), an increased risk of CHF has been observed. Findings have ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF requiring treatment or hospitalization. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease or CHF. Patients with symptomatic CHF, unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia should not be enrolled in clinical trials with ramucirumab.

Ramucirumab/placebo should be discontinued in the event of any Grade 3 or 4 events consistent with CHF.

9.A.4.1.4.2.8. Surgery and Impaired Wound Healing

Surgery and impaired wound healing have been observed with some antiangiogenic agents. Ramucirumab/placebo will not be administered to patients who have undergone major surgery within 28 days prior to randomization.

9.A.4.1.4.2.9. Liver Injury/Liver Failure

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients receiving ramucirumab. Patients with the following conditions should not be enrolled in clinical trials with ramucirumab: 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. "Clinically meaningful ascites" is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

Ramucirumab/placebo should be discontinued in the event of any new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

9.A.4.1.4.2.10. 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). Magnetic resonance imaging 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 ramucirumab clinical program, 2 blinded cases of RPLS have been reported. Both cases occurred in the ongoing double-blind, randomized, placebo-controlled Phase 3 study RAISE (I4T-MC-JVBB; IMCL CP12-0920), evaluating irinotecan, folinic acid, and 5-FU (FOLFIRI) in combination with ramucirumab 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 the potential for permanent neurological damage. Treatment encompasses careful control of blood pressure, withdrawal of potentially causative medication, and administration of anti-convulsant agents to those experiencing seizures (Stott et al. 2005).

If the diagnosis of RPLS is confirmed or is clinically indicated, ramucirumab/placebo should be permanently discontinued.

9.A.4.1.5. Recommended Dose Modification Guidelines for Chemotherapy (Part A)

The following are general principles for dose modifications of chemotherapy in Part A of the study:

- Treatment for the first cycle should only commence if all the inclusion and exclusion criteria are met and patient has been randomized to an arm of treatment via IWRS. For subsequent cycles, dose delay/modification is permitted as described in sections specific for ramucirumab/placebo (Section 9.A.4.1.4), and S-1 and oxaliplatin (Section 9.A.4.1.5). All study treatment will be discontinued in case of disease progression (Section 9.A.4.1.1).

- S-1 and oxaliplatin dose modifications are permanent; no dose escalations are allowed after dose reduction. Any patient who has had 2 dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from the study drug that is causing the toxicity. The dose of S-1 should be determined at the start of each treatment cycle.

- Doses of any study drug omitted for toxicity are not replaced or restored; instead, the patient should resume the planned treatment cycles.

- Dose modification for non-serious and non-life-threatening toxicities such as alopecia, altered taste, or nail changes may not be required; the final decision is left to the discretion of the treating investigator.

- In situations where concomitant toxicities of varying severity exist, dose modification will be tailored for the toxicity with highest NCI-CTCAE grading.

- If there is a delay or modification in administration of study drug(s) due to toxicity, treatment with the other study agent(s) should continue as scheduled. If clinically appropriate, the investigator can delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents.

- If a toxicity related to any component of chemotherapy does not resolve in the same treatment cycle, the administration of that component can be delayed up to 42 days from the next planned dose of the component. If the toxicity does not resolve within 42 days, that component will be discontinued unless it is determined by the treating investigator that the patient might benefit from continuation of the component and there are no additional safety risks involved. These situations will need to be approved by the Lilly CRP or CRS in consultation with the treating investigator.

Table JVCW.9.A.5 and Table JVCW.9.A.6 present the recommended guidelines for cycle initiation and dose modification for toxicities related to administration of S-1 and oxaliplatin in Part A of the study. Although it is recommended to refer to Table JVCW.9.A.5 and Table JVCW.9.A.6 for dose modification, the guidance of each institution can also be applied.

Table JVCW.9.A.7 presents the recommended guidelines for dose reductions of S-1 or oxaliplatin in Part A of the study.

Table JVCW.9.A.5.   Recommended Dose Modification for S-1 and Oxaliplatin (Part A)

Toxicity related to administration of S-1 and oxaliplatin	Cycle Initiation	S-1			Oxaliplatin
		Dose Omission In the Cycle	Restart In the Cycle	Dose Reduction	Dose Reduction
Leukopenia	$\geq$3000/mm^3	--	--	<1000/mm^3	<1000/mm^3
Neutropenia	$\geq$1500/mm^3	<1000/mm^3	$\geq$1000/mm^3	<500/mm^3 OR <1500/mm^3 at Day 1 of next cycle	<500/mm^3 OR <1500/mm^3 at Day 1 of next cycle
Thrombocytopenia	$\geq$75,000/mm^3	<75,000/mm^3	$\geq$75,000/mm^3	<50,000/mm^3	<75,000/mm^3 OR $\geq$75,000/mm^3, <100,000/mm^3 at Day 1 of next cycle
AST	$\leq$3.0 x ULN if no liver metastases, or $\leq$5 $\times$ ULN if liver metastases	>3.0 x ULN if no liver metastases, or >5.0 $\times$ ULN if liver metastases	$\leq$3.0 x ULN if no liver metastases, or $\leq$5.0 $\times$ ULN if liver metastases	--	--
ALT					
Serum Creatinine	<1.5 mg/dL	$\geq$1.5 mg/dL	<1.5 mg/dL	--	--
Febrile Neutropenia	--	--		Grade $\geq$3	Grade $\geq$3
Infection	No fever $\geq$38°C suspected to be caused by infection	Fever $\geq$38°C suspected to be caused by infection	No fever $\geq$38°C suspected to be caused by infection	--	--
Diarrhea	Grade $\leq$1	Grade $\geq$2	Grade $\leq$1	Grade $\geq$3	--
Mucositis/ Stomatitis	Grade $\leq$1	Grade $\geq$2	Grade $\leq$1	--	
Sensory neuropathy	Grade $\leq$2	--			-- [a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

[a]   Refer to Table JVCW.9.A.6.

Table JVCW.9.A.6. **Recommended Dose Modifications of Oxaliplatin for Treatment-Related Sensory Neuropathy (Part A)**

NCI-CTCAE[a] Grade of Sensory Neuropathy on the Day of Administration of the Subsequent Cycle	Dose Modification for Subsequent Cycles[b]
Asymptomatic; loss of deep tendon reflexes or paresthesia (Grade 1)	No change
Moderate symptoms; limiting instrumental ADL (Grade 2)	Reduce by one dose level[c]
Severe symptoms; limiting self-care ADL (Grade 3)	Skip oxaliplatin[d]
Life-threatening consequences; urgent intervention indicated (Grade 4)	Discontinue treatment[e]

Abbreviations: ADL = activities of daily living; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

[a] NCI-CTCAE v. 4.03.

[b] If the total dose of oxaliplatin exceeds 600 mg/m^2, administration of oxaliplatin can be skipped at the discretion of the investigator(s) to ensure patients' safety.

[c] The dose of oxaliplatin will not be reduced to less than 50 mg/m^2 in a patient with sensory neuropathy, and the patient will continue the treatment without further dose reduction. Dose level 0 = 100 mg/m^2; dose level –1 = 75 mg/m^2; dose level –2 = 50 mg/m^2

[d] If sensory neuropathy improves to Grade ≤2, oxaliplatin can be administered from the subsequent cycle.

[e] If Grade 4 sensory neuropathy occurs, the patient will be discontinued from study treatment at the time of confirmation of the occurrence.

Table JVCW.9.A.7. **Recommended Dose Reductions of S-1 and Oxaliplatin (Part A)**

Body surface area (m^2)	S-1			Oxaliplatin
	<1.25	1.25 - <1.5	≥1.5	
Level 0 (Initial Dose)	80 mg/day	100 mg/day	120 mg/day	100 mg/m^2 / 3 weeks
Level -1	60 mg/day	80 mg/day	100 mg/day	75 mg/m^2 / 3 weeks
Level -2	40 mg/day	60 mg/day	80 mg/day	50 mg/m^2 / 3 weeks

9.A.5. Blinding

For this study, Part A is double-blind.

The investigators and patients will remain blinded until DBL for the primary endpoint analysis is achieved (defined in Section 8.1.4). To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the database lock for the primary endpoint, PFS. Individuals (IWRS, clinical trials materials management, and data management personnel) validating the database do not have access to aggregate summary reports or statistics.

The investigator should make every effort to contact the Lilly CRP or CRS prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

If an investigator, site personnel performing assessments, or patient is unblinded before the DBL for the primary endpoint analysis for PFS, the patient must be discontinued from study treatment of Part A. In cases where there are ethical reasons to have the patient remain on study treatment

of Part A, the investigator must obtain specific approval from a CRP or CRS or designee for the patient to continue on study treatment of Part A.

9.A.5.1. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP or CRS prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

9.A.5.2. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study treatment or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP or CRS for the patient to continue in the study.

9.A.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured at each visit in the eCRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term safety follow-up visit.

A select list of restricted and excluded medications is provided in Attachment 9. No other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation (palliative radiotherapy during the study, if clinically indicated, can be considered after consultation with the Lilly CRP or CRS), or experimental medications will be permitted while patients are on study treatment. If a patient receives curative surgery for cancer while on study treatment, the patient should be discontinued from the study and receive surgery (PFS will be censored).

9.A.6.1. Supportive Care

Patients should receive full supportive care in accordance with the American Society of Clinical Oncology (ASCO; Benson et al. 2004; ASCO 2006; Smith et al. 2006; Rizzo et al. 2010) or equivalent guidelines on supportive care for solid tumors, if necessary. Supportive care measures may include, but are not limited to, antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Patients will receive supportive care as judged by their treating physician. If it is unclear

whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP or CRS. Use of any supportive care therapy should be reported on the eCRF.

Additional concurrent chemotherapy or radiation therapy (palliative radiotherapy during the study is allowed if clinically indicated and after consultation with the Lilly CRP or CRS), biologic response modifiers, or other investigational agents may not be administered to patients in this study.

9.A.6.1.1. Analgesic Agents

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 (eg, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged unless at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the patient. Chronic use of analgesic agents with no or low bleeding risk (eg, acetaminophen) is acceptable.

9.A.6.1.2. Antiemetic Therapy

The use of antiemetic agents is permitted during this study and at the discretion of the investigator. However, it is recommended to follow the guidelines of the Multinational Association of Supportive Care in Cancer and ASCO; dexamethasone may be sufficient, but 5-HT3 antagonists and NK1 antagonists may be used (ASCO 2006; Gralla et al. [WWW]).

9.A.6.1.3. Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the investigator.

9.A.6.1.4. Blood Product Transfusions

Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion during the conduct of the study.

9.A.6.1.5. Erythroid Growth Factors

The use of erythroid-stimulating factors (eg, erythropoietin or darbepoetin) is permitted at the discretion of the investigator based on ASCO and US Food and Drug Administration (FDA) guidelines (FDA [WWW]; Rizzo et al. 2010), or according to local guidelines.

9.A.6.1.6. Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

9.A.6.1.7. Granulocyte Colony-Stimulating Factors

The use of granulocyte-colony stimulating factor (G-CSF) or similar agents is permitted during study treatment at the discretion of the investigator based on ASCO (Smith et al. 2006), European Society for Medical Oncology (Crawford et al. 2009), or according to local guidelines. Prophylactic use of G-CSF or similar agents is also permitted.

9.A.6.1.8. Hypersensitivity Reactions

Premedication is required with a histamine H1 antagonist (eg, diphenhydramine hydrochloride) I.V. prior to administration of ramucirumab/placebo. Additional premedication may be provided at investigator discretion. All premedication administered must be adequately documented in the eCRF.

Patients should be premedicated with antihistamines, corticosteroids, acetaminophen, or similar after experiencing a Grade 1 or 2 IRR. If a Grade 3 or 4 IRR occurs, patients should be treated with epinephrine, bronchodilators, and/or glucocorticoids for symptomatic bronchospasm and I.V. fluids and/or pressors for hypotension.

For a second Grade 1 or 2 IRR, administer dexamethasone 8 to 10 mg I.V. (or equivalent); for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8 to 10 mg I.V. (or equivalent).

9.A.6.2. Concomitant Therapy to Use with Caution

When the following therapies are administered in combination with ramucirumab, special attention is needed as described below.

- Aspirin up to 325 mg/day is permitted. The use of analgesic agents is permitted at the discretion of the investigator. The chronic use of NSAIDs with a high risk of bleeding (eg, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged, unless at the discretion and responsibility of the investigator, after careful assessment of the individual bleeding risk of the patient. Chronic use of analgesic agents with no or low bleeding risk (eg, acetaminophen) is acceptable.
- Anticoagulation agents, such as other low-dose anticoagulation therapies are permitted; however, warfarin is not permitted.
- Chronic use of antiplatelet agents (eg, clopidogrel, ticlopidine, dipyridamole, and anagrelide) is not permitted.

9.A.7. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by direct questioning, review of diary, and counting returned study medication.

The following procedures will be employed to assure appropriate drug accountability:

- Drug accountability will be emphasized at the start-up meeting.
- Drug accountability will be monitored throughout the study.
- Each patient will be instructed to return all study drug packaging and unused material to the study site at each visit. The study site will keep a record of all study drug dispensed to and returned by the patients throughout the study. Study site personnel will return all unused study drug for all patients.
- Each patient will be instructed to keep a study diary to document that he/she is taking the study drug correctly.

The patient must take ≥80% to ≤100% of the intended dose to be deemed compliant with administration of S-1. Similarly, a patient may be considered noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken less or more than the prescribed amount of S-1 (ie, <80% or >100%). Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP or CRS before the final determination is made to discontinue the patient.

9.B. Treatment of Part B

9.B.1. Treatments Administered

Upon completion of assessments of pre-treatment period of Part B, eligible patients with metastatic gastric or GEJ adenocarcinoma will be treated with ramucirumab plus paclitaxel (Part B).

Principally, a cycle is defined as an interval of 28 days in Part B (Note: A delay due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 days and not be counted as a protocol deviation. Additionally, in a circumstance where Lilly confirms that a delay will be permitted over 3 days, such as a New Year's holiday or similar, this instance will not be counted as a protocol deviation.). In Part B, a cycle will begin at the Day 1 administration of paclitaxel treatment.

For Part B, patients in both treatment arms will receive ramucirumab followed by paclitaxel. In the initial 2 administrations of ramucirumab, patients will receive paclitaxel after the 1-hour observation period. If there is no evidence of an IRR during the initial 2 administrations, then no observation period is required for subsequent administrations. In the event that an IRR occurs thereafter, then the approximately 1-hour observation should be reinstituted.

Premedication is required prior to infusion of ramucirumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at investigator discretion. See also Section 9.B.4.1.5.1 for premedication guidelines for Grade 1 or 2 IRRs. All premedication administered must be adequately documented in the eCRF.

Figure JVCW.9.B.2 illustrates and Table JVCW.9.B.8 presents the treatment regimens/dosing schedule for Part B.
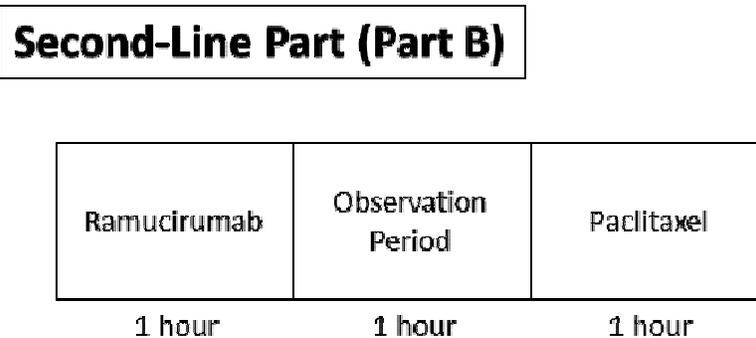
Figure JVCW.9.B.2.   Illustration of treatment regimen/dosing schedule for Part B.

Table JVCW.9.B.8.   Treatment Regimens/Dosing Schedule

Part B (28-day Cycle)		
Drug[a]	**Dose**	**Time for Administration**
Ramucirumab[b,c]	8 mg/kg I.V.	Administered over approximately 60 min on Day 1 and Day 15
Paclitaxel	80 mg/m^2 I.V.	Administered over 60 min on Day 1, Day 8, and Day 15

Abbreviation: I.V. = intravenously.

Note: All treatments are administered in the order shown in the table.

[a] Ramucirumab and paclitaxel will be administered until disease progression or other withdrawal criteria are met.

[b] Premedication with an intravenous histamine H1 antagonist, such as diphenhydramine hydrochloride (or equivalent), is required prior to infusion of ramucirumab for Part B. See also Section 9.B.4.1.5.1 for premedication guidelines for Grade 1 or 2 infusion-related reactions.

[c] A 1-hour observation period following the ramucirumab infusion is mandatory for the first 2 administrations. If there is no evidence of an infusion-related reaction to ramucirumab after the administration of the first 2 administrations, then no observation period is required for subsequent administrations. Administration of antiemetics can occur during this same time period (see Section 9.B.6.1.2).

Dose reductions of investigational product and/or chemotherapy will be made in the event of specific treatment-related AEs, as described in Section 9.B.4.1. Supportive care guidelines are detailed in Section 9.B.6.1.

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 patient/site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of IP 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 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.

All products will be administered according to the instructions below.

9.B.1.1. Premedication

9.B.1.1.1. Premedication Prior to Infusion of Ramucirumab

Premedication with an I.V. histamine H1 antagonist, such as diphenhydramine hydrochloride (or equivalent), is required prior to infusion of ramucirumab. Additional premedication may be provided at investigator discretion. See also Section 9.B.4.1.5.1 for premedication guidelines for Grade 1 or 2 IRRs. All premedication administered must be adequately documented in the eCRF.

9.B.1.2. Preparation and Administration of Ramucirumab

Aseptic technique is to be used when preparing and handling ramucirumab for infusion. Patients will receive ramucirumab by I.V. infusion over approximately 60 minutes at 8 mg/kg on Day 1 and Day 15 every 28 days (Part B) in the absence of disease progression or until other withdrawal criteria are met. The first dose of ramucirumab administered in Part B is dependent upon the patient's body weight in kilograms during the pre-treatment period of Part B. Patients should be weighed at the beginning of each cycle (defined in the Study Schedule; Attachment 1). If there is a ≥10% change (increase or decrease) in body weight from the last dose calculation, then the dose of ramucirumab **must** be recalculated. 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.

Ramucirumab is compatible with common infusion containers. Details regarding infusion sets that are compatible for ramucirumab infusion can be found in the JVCW Additional Pharmacy/Dispensing Instructions and the IB.

Based on the calculated volume of ramucirumab, add (or remove from pre-filled [with 0.9% normal saline] I.V. infusion container) a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to make the total volume 250 mL. For dose volumes greater than 250 mL, the addition of sterile normal saline is not required. Do not use dextrose-containing solutions. The container should be gently inverted to ensure adequate mixing. The infusion should be delivered via infusion pump in approximately 60 minutes. The infusion rate should not exceed 25 mg/minute. Infusions of duration longer than 60 minutes are permitted in specific circumstances (ie, for larger patients in order to maintain an infusion rate that does not exceed 25 mg/minute, or in the setting of prior ramucirumab IRR); the infusion duration must always be accurately recorded. The infusion set must be flushed post infusion with sterile 0.9% normal saline equal to or greater than infusion set hold-up volume to ensure delivery of the calculated dose.

See Section 9.B.1.1.1 for premedication guidelines prior to infusion of ramucirumab.

CAUTION: IRRs may occur during or following ramucirumab administration (see Attachment 8 for a definition of Grade 3 and 4 IRRs). During the administration of ramucirumab, patients should be in an area with resuscitation equipment and treatments necessary for advanced life support and cardiopulmonary resuscitation, such as bronchodilators, vasopressor agents (eg, epinephrine), oxygen, glucocorticoids, antihistamines, I.V. fluids, and so forth. A 1-hour observation period is required after the administration of the initial 2 administrations of ramucirumab in Part B. If there is no evidence of an IRR during the initial 2 administrations of ramucirumab, then no observation period is required for subsequent administrations. In the event that an IRR occurs thereafter, the 1-hour observation should be reinstituted.

9.B.1.3. Preparation and Administration of Paclitaxel

Investigators should consult the manufacturer's instructions for paclitaxel for complete prescribing information and follow institutional procedures for the administration of paclitaxel.

Patients will receive paclitaxel by I.V. infusion over approximately 60 minutes at 80 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle. Note that the same formula is to be used for body surface area during the treatment period of Part B.

9.B.2. Materials and Supplies

Ramucirumab will be provided by Lilly. Paclitaxel will be obtained locally. Clinical trial materials provided by Lilly will be labeled according to the country's regulatory requirements.

9.B.2.1. Ramucirumab

Ramucirumab is a sterile, preservative-free solution for infusion of ramucirumab formulated in an aqueous solution at a concentration of 10 mg/mL (500 mg/50-mL vial). The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80, pH 6.0.

All excipients used for the manufacture of ramucirumab are of pharmacopeial grade. No animal-derived components are used in the manufacture of ramucirumab excipients.

Refer to the current version of the ramucirumab IB for safe handling and administration details.

9.B.2.2. Chemotherapy Agents

Commercial preparations of paclitaxel will be used in this study, and will be packaged, labeled, and stored according to manufacturer standards and according to the country's regulatory requirements, if supplied by the sponsor.

9.B.3. Method of Assignment to Treatment

Patients who meet initiation criteria of Part B (see Table JVCW.9.B.9) will be assigned to receive study treatment of Part B via the IWRS.

9.B.4. Selection and Timing of Doses

A cycle is defined as an interval of 28 days in Part B (Note: A delay due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 days and not be counted as a protocol deviation. Additionally, in a circumstance where Lilly confirms that a delay will be permitted over 3 days, such as a New Year's holiday or similar, this instance will not be counted as a protocol deviation.). A cycle will begin at the Day 1 administration of paclitaxel treatment. If a patient discontinues any component of study treatment, Day 1 will be based on the administration of the remaining study component. In case a patient receives only ramucirumab monotherapy because the patient doesn't meet initiation criteria of paclitaxel (see Table JVCW.9.B.9), Day 1 will be based on the administration of ramucirumab (28 days) until starting combination therapy of paclitaxel and ramucirumab.

Patients may continue to receive ramucirumab and paclitaxel in Part B until 1 or more of the specified reasons for discontinuation are met (as described in Section 7.3).

9.B.4.1. Special Treatment Considerations

9.B.4.1.1. Transition from Part A to Part B

The pre-treatment period of Part B begins the day after the decision is made that the patient will no longer continue study treatment of Part A. Patients who meet initiation criteria of Part B can start administration of study treatment of Part B.

Patients who transition from Part A to Part B should keep the following period from last dose of Part A to first dose of Part B for each drug.

- Ramucirumab/placebo: cannot be administered in consecutive 3 weeks

- S-1: 1 week from last dose of S-1 to first dose of paclitaxel

- Oxaliplatin: 3 weeks from last dose of oxaliplatin to first dose of paclitaxel.

Table JVCW.9.B.9 presents the initiation criteria of Part B.

Table JVCW.9.B.9.   Initiation Criteria of Part B

Criteria for Ramucirumab treatment	Ramucirumab related toxicities/AEs:	Grade <2 or baseline (except for hypertension, venous thromboembolic events, and proteinuria)
	Urine protein:	Dipstick <2+ In case of dipstick ≥2+, perform a 24-hour urine collection or urine protein/creatinine ratio, and the 24-hour collection or urine protein/creatinine ratio need to show protein level <2 g/24 h.
Criteria for Paclitaxel treatment	Toxicities/AEs:	Grade <2 of all clinically significant toxicity of Part A treatment Even if a patient shows grade 2 of toxicity (eg, neuropathy, alopecia, or dysgeusia), paclitaxel treatment of Part B can be started at investigator discretion.
	Neutrophils:	≥1500/mm^3
	Platelets:	≥100,000/mm^3
	Serum Creatinine:	<1.5 x ULN or calculated creatinine clearance ≥50 mL/min
	Bilirubin:	≤1.5 × ULN
	AST/ALT:	≤3 × ULN if no liver metastases, or <5 × ULN if liver metastases

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Patients who do not meet the initiation criteria of Part B within 12 weeks from decision of study treatment discontinuation of Part A should be discontinued from study.

If ramucirumab/placebo was permanently discontinued in Part A, ramucirumab cannot be administered in Part B. In this case, patients can start Part B treatment with paclitaxel only. Even if the ramucirumab dose is reduced in Part A, ramucirumab can be started at 8 mg/kg from

the beginning of Part B. When appropriate, ramucirumab dose of Part B can start with the dose which was reduced in Part A (ie, 6 mg/kg or 5 mg/kg).

In the case where a patient does not meet the treatment criteria for ramucirumab or paclitaxel in Part B, the patient has the option to start Part B treatment with either ramucirumab or paclitaxel administration. The other study drug can be administered once the patient has recovered from the prior toxicities/AEs.

9.B.4.1.2. Discontinuation from Part B

Patients will be discontinued from study treatment of Part B in the following circumstances:

- Any study treatment-related event that is deemed life-threatening if the event is considered possibly related to any components of study therapy.

- Any unacceptable AE/toxicity (eg, a persistent moderate toxicity that is intolerable to the patient)

- Evidence of progressive disease per RECIST v1.1 criteria.

    o **Note:** Discontinuation from all or any study treatment for reasons other than radiographically confirmed PD should be based on strong clinical justification. If discontinuation is required (eg, due to toxicity), investigators should consider an initial discontinuation of one study agent, followed by the additional agent(s) if required.

- The investigator decides that the patient should be discontinued from study treatment in Part B.

- The patient requests to be withdrawn from study treatment in Part B.

If 1 therapeutic agent is permanently discontinued, then treatment with the other study agent should continue and the patient should remain on study with full adherence to all protocol-related requirements as clinically appropriate.

Study blinding will continue through disease progression/subsequent lines of treatment until DBL for the primary endpoint analysis is achieved (see Section 8.1.4). Lilly will not supply ramucirumab or any other study drugs outside of the study treatment schedule as defined in Section 8.1.

9.B.4.1.3. Discontinuation of Ramucirumab (Part B)

Patients will be discontinued from ramucirumab for any of the following reasons:

- **ATE:** Any Grade 3-4 ATE;

- **Severe bleeding:** Grade 3-4 bleeding due to any reason;

- **Hypertension** that cannot be medically controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy;

- **IRR:** Any Grade 3-4 IRR that is clearly attributed to ramucirumab;

- **Gastrointestinal perforation** or **fistulae**: Any grade GI perforation or fistulae;

- **New occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis**;

- **RPLS**;

- **Urine protein**: level of ≥3 g/24 hours or in the setting of nephrotic syndrome;

- **Dose modifications**: >2 dose reductions.

- **VTE:** A Grade 3-4 VTE occurs that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy;

- **Impaired wound healing:** Discontinue ramucirumab if wound is not fully healed within 42 days withholding from the next planned dose of ramucirumab;

- **Any Grade 4 (life-threatening) nonhematologic toxicity** considered by the investigator to be possibly, probably, or definitely related to ramucirumab;

- **Any PE/DVT** occurring or intensifying during anticoagulant therapy;

- **CHF:** Any Grade 3-4 events that are consistent with CHF.

Patients who are discontinued from ramucirumab will continue to be in the study, and should continue to receive paclitaxel treatment (if appropriate), in accordance with the protocol. If an existing AE related to ramucirumab treatment in Part A exacerbates during Part B, the investigator should evaluate if continuation of ramucirumab is clinically justified.

9.B.4.1.4. Discontinuation of Paclitaxel in Part B
Patients will be discontinued from paclitaxel in Part B for the following reason:

- **Dose modifications:** >2 dose reductions.

Patients who are permanently discontinued from paclitaxel in Part B will continue to be in the study, and should continue to receive ramucirumab treatment (if appropriate), in accordance with this protocol.

The criteria for dose modifications due to AEs related to paclitaxel (Part B) are described in Section 9.B.4.1.5.

9.B.4.1.5. Recommended Dose Modification Guidelines for Ramucirumab and Paclitaxel (Part B)

The following are general principles for dose modifications for ramucirumab and paclitaxel in Part B of the study:

- No dose modification for paclitaxel is allowed within a given cycle. The paclitaxel dose will be reduced by 10 mg/m^2 for the following cycle when Grade 4 hematological toxicity or Grade 3 paclitaxel-related nonhematological toxicity (except for alopecia) is observed. If the dose of paclitaxel is reduced because of potentially related AEs, subsequent dose increases are not permitted. Paclitaxel will be permanently discontinued if dose reduction to less than 60 mg/m^2 would be required, or in case of any paclitaxel-related event that is deemed life-threatening, regardless of grade.

- In the event that administration of paclitaxel is delayed or skipped due to paclitaxel-related toxicity, the start of the next cycle will be delayed until recovery. However, ramucirumab should continue as scheduled until the next cycle has resumed. When the subsequent cycle of paclitaxel is initiated, administration of ramucirumab and paclitaxel will be resynchronized (ie, the cycle will begin at Day 1 for both ramucirumab and paclitaxel, even if this requires ramucirumab to be administered on consecutive weeks). In case of discontinuation of paclitaxel for any reason, a new cycle will be started on Day 29 (Day 1 of the new cycle) with the administration of ramucirumab monotherapy.

- In the event of paclitaxel-related toxicity on Day 8 or 15, paclitaxel will be skipped at that day. No dose reductions are allowed within a given cycle.

- In the event of ramucirumab-related toxicity, ramucirumab will be delayed for 1 week and administered the next week, provided that ramucirumab-related toxicities have resolved to Grade <2 or baseline (except for hypertension, VTEs, and proteinuria). If toxicities have not resolved, ramucirumab will be delayed for another week and administered the next week. If toxicities have not resolved on Day 22, ramucirumab will be skipped for that cycle and administered on Day 1 of the following cycle provided that ramucirumab-related toxicities have resolved to Grade <2 or baseline. In any cases, paclitaxel will continue according to the planned schedule.

- If a patient cannot be treated with 1 component of the study therapy (ie, paclitaxel or ramucirumab) for more than 56 days from the last administered dose, that component will be permanently discontinued. The other agent should be continued, with the patient remaining on study, if clinically indicated.

9.B.4.1.5.1. Recommended Dose Modification Guidelines for Ramucirumab for Specific Adverse Events (Part B)

Table JVCW.9.B.10 presents the recommended dose modification guidelines for specific AEs related to administration of ramucirumab in Part B of the study.

Table JVCW.9.B.10.   Recommended Dose Modification Guidelines for Ramucirumab for Specific Adverse Events – Part B

Toxicity related to administration of ramucirumab			Gr	Dose Adjustment for Ramucirumab
Reversible, non-life-threatening toxicity (eg, fatigue/anorexia/fever/laboratory abnormalities [a]). For hypertension, see below.	First instance		3/4	8 mg/kg (full dose) on recovery to Grade ≤1
	Second instance		3/4	6 mg/kg (first dose reduction) for next dose on recovery to Grade ≤1
	Third instance		3/4	5 mg/kg (second dose reduction) for next dose on recovery to Grade ≤1
	Subsequent instance		3/4	Discontinue (if a third dose reduction is required) (see Section 9.B.4.1.3)
Infusion-related reactions			1-2	If clinically indicated, stop the infusion temporarily and then reduce the infusion rate of ramucirumab by 50%.
			3/4	Discontinue (see Section 9.B.4.1.3)
Hypertension	**Hypertension controlled with medications**		1	8 mg/kg (full dose) without interruption
	Hypertension (non-life threatening and symptomatic)	Resolution to Grade <2 within 3 weeks	2/3	Delay ramucirumab administration. Administer 8 mg/kg (full dose) once hypertension is controlled with medications and is Grade <2 within 3 weeks.
		Resolution to Grade <2 within 3 to 6 weeks	2/3	Delay ramucirumab administration. Administer ramucirumab at 6 mg/kg if hypertension is Grade <2 by the fourth week. Administer ramucirumab at 5 mg/kg if hypertension is Grade <2 by the sixth week. Discontinue ramucirumab if blood pressure does not improve to Grade <2 by the sixth week (42 days from the next planned dose of ramucirumab).
	Uncontrolled hypertension, hypertensive crisis, hypertensive encephalopathy		4	Discontinue (see Section 9.B.4.1.3)
Congestive heart failure			3/4	Discontinue (see Section 9.B.4.1.3)

Recommended Dose Modification Guidelines for Ramucirumab for Specific Adverse Events – Part B

Toxicity related to administration of ramucirumab			Gr	Dose Adjustment for Ramucirumab
Proteinuria **Note:** Protein algorithm is provided in Attachment 10.	**Proteinuria (dipstick <2+)**			Administer baseline or full previous dose of ramucirumab without interruption.
	Proteinuria (dipstick 2+)			Administer full previous dose of ramucirumab without interruption. Perform a 24-hour urine collection within 3 days prior to next ramucirumab dose administration.[c] If the 24-hour collection shows proteinuria <2 g/24 hours, administer unchanged dose of ramucirumab. If $\geq$ 2g/24 hours, then follow dose adjustment based on 24-hour collection (below).
	Proteinuria (dipstick >2+)			Delay ramucirumab administration. Perform a 24-hour urine collection within 3 days prior to ramucirumab administration.[c] If the 24-hour collection shows proteinuria <2 g, administer unchanged dose of ramucirumab. If $\geq$2 g, then follow dose adjustment based on 24-hour collection (below).
	Proteinuria based on 24-hour urine collection $\geq$2 g/24 hours[b,c]	First instance		6 mg/kg once urinary protein returns to <2 g/24 hours
		Second instance		5 mg/kg once urinary protein returns to <2 g/24 hours
		Third instance		Discontinue (if a third dose reduction is required) (see Section 9.B.4.1.3)
	Proteinuria based on 24-hour urine collection >3 g/24 hours[b,c] or in the setting of nephrotic syndrome			Discontinue (see Section 9.B.4.1.3)
Arterial thromboembolic events, venous thromboembolic events, or bleeding			3/4	Discontinue (see Section 9.B.4.1.3)
Gastrointestinal perforation or fistulae			Any	Discontinue (see Section 9.B.4.1.3)
RPLS				Discontinue (see Section 9.B.4.1.3)
Liver injury/liver failure			Any	Discontinue (see Section 9.B.4.1.3)

Recommended Dose Modification Guidelines for Ramucirumab for Specific Adverse Events – Part B
Abbreviations: Gr = grade; RPLS = reversible posterior leukoencephalopathy syndrome.

a Dose modifications are not required for hematologic laboratory abnormalities unless associated with clinical symptoms. As an initial step, the dose of chemotherapy should be reduced first before any dose reductions for ramucirumab are considered.

b A dipstick test for proteinuria should be performed prior to each infusion of ramucirumab. If both dipstick and 24-hour tests are performed, the results of 24-hour collection should be used for clinical decision-making.

c Although it is recommended to perform a 24-hour urine collection, urine protein/creatinine ratio measured in urine sample can be used to check the urine protein level if implementation of 24-hour urine collection is difficult. In the event that the urine protein/creatinine ratio is 1, 24-hour urine collection will be 1 g/24 hours.

9.B.4.1.5.2. Treatment Guidelines for Specific Adverse Events Related to Ramucirumab (Part B)

Adverse events of special interest which may or may not be associated with ramucirumab therapy may include IRRs, hypertension, ATEs, VTEs, bleeding (hemorrhagic) events, GI perforation, proteinuria, CHF, surgery and impaired wound healing, liver injury/liver failure, and RPLS.

9.B.4.1.5.2.1. Infusion-Related Reactions

Any treatment-related IRRs are defined according to the NCI-CTCAE v. 4.03 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. Those IRRs described above should be graded as shown in Attachment 8.

Consistent with usual medical practice, the patient should be clinically monitored and selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below. The Lilly CRP, CRS, or designee should be contacted immediately if questions arise concerning the grade of the reaction.

The following are treatment guidelines for IRRs.

Clinical and laboratory monitoring:

- Time (24-hour clock)

- Body temperature in Celsius

- Arterial pulse rate in beats per minute

- Respiratory rate per minute

- Systolic blood pressure in mm Hg

- Diastolic blood pressure in mm Hg

- Other investigations as clinically necessary (eg, oxygen saturation, chest x-ray, ECG)

- All attempts should be made to obtain a blood sample for anti-ramucirumab antibody analysis as close to the onset of the event as possible, at the resolution of the event, and approximately 30 days following the event. Additional samples may be assessed for levels of ramucirumab and other tests to provide information on the nature of the IRR.

Grade 1 IRR

- Slow the infusion rate by 50%.

- Monitor the patient for worsening of condition.

- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion.

Grade 2 IRR

- Stop the infusion.

- Administer I.V. diphenhydramine hydrochloride 50 mg (or equivalent), acetaminophen 650 mg orally for fever, and oxygen.

- Resume the infusion at 50% of the prior rate once the IRR has resolved or decreased to Grade 1; the infusion duration should not exceed 2 hours.

- Monitor for worsening of condition.

- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent); additional premedication may be administered at the investigator's discretion.

For a second Grade 1 or 2 IRR, administer I.V. dexamethasone 8-20 mg (or equivalent); for subsequent infusions, premedicate with I.V. diphenhydramine hydrochloride 50 mg (or equivalent), acetaminophen 650 mg orally, and I.V. dexamethasone 8-20 mg (or equivalent).

Grade 3 or Grade 4 IRR

- Stop the infusion and disconnect the infusion tubing from the patient.

- Administer I.V. diphenhydramine hydrochloride (or equivalent, per institutional guidelines), I.V. dexamethasone (or equivalent, per institutional guidelines), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.

- Give epinephrine or bronchodilators as indicated.

- Hospital admission for observation may be indicated.

- Patients who have a Grade 3 or 4 IRR will not receive further ramucirumab treatment, but will continue to be followed on the protocol.

9.B.4.1.5.2.2. Hypertension

The following are general treatment guidelines for hypertension (an expected AE in patients receiving ramucirumab) during the study. Uncontrolled hypertension is defined as Grade >2 in NCI-CTCAE v. 4.03 (the patient continues to clinically experience raised blood pressure [systolic ≥160 mm Hg and/or diastolic ≥100 mm Hg] despite medications). Every attempt should be made to control the blood pressure to systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg prior to starting treatment with ramucirumab. Investigators have the discretion to consider the clinical circumstances of individual patients, especially involving borderline hypertension, and to administer unchanged doses of ramucirumab for blood pressure up to systolic blood pressure 150 mm Hg and diastolic blood pressure 90 mm Hg, if clinically appropriate. Routine clinical and laboratory monitoring is highly recommended in patients who develop de novo hypertension or experience a deterioration in previous hypertension. Control hypertension prior to initiating treatment with ramucirumab. Monitor blood pressure prior to every administration of ramucirumab or more frequently as indicated during treatment. For dose modifications guidelines, refer to Table JVCW.9.B.10.

Grade 1 hypertension

- Continue ramucirumab therapy at baseline or previous dose. Initiate or continue antihypertensive therapy if clinically indicated.

Grade 2 or Grade 3 hypertension

- If the hypertension is not associated with symptoms, continue ramucirumab therapy and initiate or continue antihypertensive therapy.

- If the hypertension is associated with symptoms, hold ramucirumab therapy and initiate or continue antihypertensive therapy until symptoms resolve to Grade <2 (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg)

- If ramucirumab administration is interrupted due to hypertension or related symptoms,

  o review blood pressure once a week for 3 weeks, and if Grade <2 administer previous dose of ramucirumab.

  o if blood pressure improves to Grade <2 by the fourth week, reduce ramucirumab dose to 6 mg/kg on Day 1 and Day 8.

  o if blood pressure improves to Grade <2 by the sixth week, reduce ramucirumab dose to 5 mg/kg on Day 1 and Day 8.

  o if blood pressure does not improve to Grade <2 by the sixth week (42 days from the next planned dose of ramucirumab), discontinue ramucirumab.

<u>Grade 4 or refractory hypertension</u>

- Patients with Grade 4 hypertension (life-threatening consequences; for example, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis; or urgent intervention indicated) or patients whose hypertension is poorly controlled ($\geq$160 mm Hg systolic or $\geq$100 mm Hg diastolic for >6 weeks [>42 days from the next planned dose of ramucirumab]) despite appropriate oral medication (eg, 2 or more oral agents at maximum tolerated dose) will be discontinued from ramucirumab.

9.B.4.1.5.2.3. Thromboembolic Events

Investigators should perform all testing required to fully characterize ATEs or VTEs. The incidence and type of thrombotic/vascular events will be collected and reported.

Ramucirumab therapy should be discontinued in the event of any Grade 3 or 4 ATE or VTE that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy. At the investigator's discretion, ramucirumab therapy may be continued in the setting of an incidentally diagnosed, asymptomatic DVT or PE or following a symptomatic DVT or PE when symptoms have resolved with the institution of anticoagulation therapy.

Ramucirumab should also be discontinued in the setting of a DVT or PE that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

9.B.4.1.5.2.4. Bleeding (Hemorrhagic) Events

Serious hemorrhagic AEs have been reported from clinical studies investigating ramucirumab. Hemorrhagic complications are associated with some malignancies (ie, 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 precludes any definitive association between bleeding and ramucirumab. Ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential and is detailed in the inclusion/exclusion criteria.

Discontinue ramucirumab in the event of a Grade 3 or 4 bleeding (hemorrhagic) event.

9.B.4.1.5.2.5. Proteinuria

If, while on ramucirumab therapy, a patient has proteinuria $\geq$2+ per a dipstick or routine urinalysis test, a 24-hour urine collection will be conducted. If the protein level is <2 g/24 hours, the patient will continue on ramucirumab therapy at the same dose without interruption.

If the dipstick is 2+, administer full previous dose of ramucirumab without interruption. Perform a 24-hour urine collection within 3 days prior to next ramucirumab dose administration. If the 24-hour collection shows proteinuria <2 g/24 hours, administer unchanged dose of ramucirumab. If the protein level is $\geq$2 g/24 hours, delay ramucirumab administration and perform a 24-hour urine collection prior to the next planned dose of ramucirumab. Ramucirumab treatment will

resume at a reduced dose level (6 mg/kg) once the protein level returns to <2 g/24 hours. A second dose reduction of ramucirumab to 5 mg/kg is permitted in case of a second instance of proteinuria ≥2 g/24 hours. The patient will be discontinued from ramucirumab treatment if the protein level is >3 g/24 hours, if there is a third occurrence of proteinuria ≥2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 42 days of interruption from the next planned dose of ramucirumab.

For dose modification guidelines, refer to Table JVCW.9.B.10.

9.B.4.1.5.2.6. 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.

Patients with a history of GI perforation within 6 months prior to randomization are excluded from participation (see Section 7.2). Ramucirumab should be permanently discontinued in the event of a GI perforation.

9.B.4.1.5.2.7. Congestive Heart Failure

In patients who received ramucirumab in combination with mitoxantrone (Study JVBS, in patients with androgen-independent prostate cancer) or following prior anthracycline therapy (Study JVBX, in patients with locally advanced or metastatic breast cancer), an increased risk of CHF has been observed. Findings have ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF requiring treatment or hospitalization. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease or CHF. Patients with symptomatic CHF, unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia should not be enrolled in clinical trials with ramucirumab.

Ramucirumab should be discontinued in the event of any Grade 3 or 4 events consistent with CHF.

9.B.4.1.5.2.8. Surgery and Impaired Wound Healing

Surgery and impaired wound healing have been observed with some antiangiogenic agents. Ramucirumab will not be administered to patients who have undergone major surgery within 28 days prior to randomization.

9.B.4.1.5.2.9. Liver Injury/Liver Failure

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients receiving ramucirumab. Patients with the following conditions should not be enrolled in clinical trials with ramucirumab: 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. "Clinically meaningful ascites" is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

Ramucirumab should be discontinued in the event of any new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

9.B.4.1.5.2.10. 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). Magnetic resonance imaging 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 ramucirumab clinical program, 2 blinded cases of RPLS have been reported. Both cases occurred in the ongoing double-blind, randomized, placebo-controlled Phase 3 study RAISE (I4T-MC-JVBB; IMCL CP12-0920), evaluating irinotecan, folinic acid, and 5-FU (FOLFIRI) in combination with ramucirumab 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 the potential for permanent neurological damage. Treatment encompasses careful control of blood pressure, withdrawal of potentially causative medication, and administration of anti-convulsant agents to those experiencing seizures (Stott et al. 2005).

If the diagnosis of RPLS is confirmed or is clinically indicated, ramucirumab should be permanently discontinued.

9.B.4.1.6. Criteria for Starting Next Cycle (Part B)

Table JVCW.9.B.11 presents the recommended guidelines for starting the next cycle of ramucirumab for specific AEs related to administration of ramucirumab in Part B of the study.

Table JVCW.9.B.11. **Criteria for Ramucirumab Treatment – Part B**

Urine protein:	Dipstick ≤2+
	In case of dipstick 2+, perform a 24-hour urine collection or urine protein/creatinine ratio within 3 days prior to next ramucirumab dose administration, and the 24-hour collection or urine protein/creatinine ratio need to show protein level <2 g/24 h.
Ramucirumab related toxicities/AEs:	Grade <2 or baseline (except for hypertension, venous thromboembolic events, and proteinuria)

Abbreviation: AE = adverse event.

Table JVCW.9.B.12 and Table JVCW.9.B.13 present the recommended guidelines of starting the next cycle of paclitaxel in Part B of the study.

Table JVCW.9.B.12. **Criteria for Paclitaxel Treatment (Day 1 Administration) – Part B**

Neutrophils:	≥1500/mm³
Platelets:	≥100,000/mm³
Serum Creatinine:	<1.5 x ULN or calculated creatinine clearance ≥50 mL/min
Bilirubin:	≤1.5 × ULN
AST/ALT:	≤3 × ULN if no liver metastases, or <5 × ULN if liver metastases
Paclitaxel-related Toxicities/AEs:	Grade <2 or baseline (except for alopecia) Anemia Grade ≤2

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Table JVCW.9.B.13. **Criteria for Paclitaxel Treatment (Day 8 and Day 15 Administration) – Part B**

Neutrophils:	≥1000/mm³
Platelets:	≥75,000/mm³
Bilirubin:	≤1.5 × ULN
AST/ALT:	≤3 × ULN, or <5 × ULN if the aminotransferase elevation is due to liver metastases
Paclitaxel-related Toxicities/AEs:	Grade <2 or baseline (except for alopecia) Anemia Grade ≤2

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

9.B.5. Blinding

For this study, Part B is open-label.

9.B.5.1. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP or CRS prior to

unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

Study treatment is not to be unblinded for progressive disease or transition to Part B. All calls resulting in an unblinding event are recorded and reported by the IWRS.

9.B.5.2. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel performing assessments, or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study treatment or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue on study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP or CRS for the patient to continue in the study.

9.B.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured at each visit in the eCRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term safety follow-up visit.

A select list of restricted and excluded medications is provided in Attachment 9. No other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation (palliative radiotherapy during the study, if clinically indicated, can be considered after consultation with the Lilly CRP or CRS), or experimental medications will be permitted while patients are on study treatment. If a patient receives curative surgery for cancer while on study treatment, the patient should be discontinued from the study and receive surgery (PFS will be censored).

9.B.6.1. Supportive Care

Patients should receive full supportive care in accordance with ASCO (Benson et al. 2004; ASCO 2006; Smith et al. 2006; Rizzo et al. 2010) or equivalent guidelines on supportive care for solid tumors, if necessary. Supportive care measures may include but are not limited to antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Patients will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP or CRS. Use of any supportive care therapy should be reported on the eCRF.

Additional concurrent chemotherapy or radiation therapy (palliative radiotherapy during the study is allowed if clinically indicated and after consultation with the Lilly CRP or CRS), biologic response modifiers, or other investigational agents may not be administered to patients in this study.

9.B.6.1.1. Analgesic Agents

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 (eg, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged unless at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the patient. Chronic use of analgesic agents with no or low bleeding risk (eg, acetaminophen) is acceptable.

9.B.6.1.2. Antiemetic Therapy

The use of antiemetic agents is permitted during this study and at the discretion of the investigator. However, it is recommended to follow the guidelines of the Multinational Association of Supportive Care in Cancer and ASCO; dexamethasone may be sufficient, but 5-HT3 antagonists and NK1 antagonists may be used (ASCO 2006; Gralla et al. [WWW]).

9.B.6.1.3. Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the investigator.

9.B.6.1.4. Blood Product Transfusions

Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion during the conduct of the study.

9.B.6.1.5. Erythroid Growth Factors

The use of erythroid-stimulating factors (eg, erythropoietin or darbepoetin) is permitted at the discretion of the investigator based on ASCO and FDA guidelines (FDA [WWW]; Rizzo et al. 2010), or according to local guidelines.

9.B.6.1.6. Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy.

9.B.6.1.7. Granulocyte Colony-Stimulating Factors

The use of G-CSF or similar agents is permitted during study treatment at the discretion of the investigator based on ASCO (Smith et al. 2006), European Society for Medical Oncology (Crawford et al. 2009), or according to local guidelines. Prophylactic use of G-CSF or similar agents is also permitted.

9.B.6.1.8. Hypersensitivity Reactions

Premedication is required with a histamine H1 antagonist (eg, diphenhydramine hydrochloride) I.V. prior to administration of ramucirumab/placebo in both Part A and Part B. Additional premedication may be provided at investigator discretion. All premedication administered must be adequately documented on the eCRF.

Patients should be premedicated with antihistamines, corticosteroids, acetaminophen, or similar after experiencing a Grade 1 or 2 IRR. If a Grade 3 or 4 IRR occurs, patients should be treated with epinephrine, bronchodilators, and/or glucocorticoids for symptomatic bronchospasm and I.V. fluids and/or pressors for hypotension.

For a second Grade 1 or 2 IRR, administer dexamethasone 8 to 10 mg I.V. (or equivalent); for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg I.V. (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8 to 10 mg I.V. (or equivalent).

9.B.6.2. Concomitant Therapy to Use with Caution

When the following therapies are administered in combination with ramucirumab, special attention is needed as described below.

- Aspirin up to 325 mg/day is permitted.   The use of analgesic agents is permitted at the discretion of the investigator. The chronic use of NSAIDs with a high risk of bleeding (eg, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged, unless at the discretion and responsibility of the investigator, after careful assessment of the individual bleeding risk of the patient. Chronic use of analgesic agents with no or low bleeding risk (eg, acetaminophen) is acceptable.
- Anticoagulation agents, such as other low-dose anticoagulation therapies are permitted; however, warfarin is not permitted.
- Chronic use of antiplatelet agents (eg, clopidogrel, ticlopidine, dipyridamole, and anagrelide) is not permitted.

9.B.7. Treatment Compliance

The study medication for Part B will be administered only at the investigational sites by authorized study personnel. As a result, a patient's compliance with study drug administration is ensured.

10. Efficacy, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

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

Radiologic assessments obtained previously as part of routine clinical care may be used as the baseline assessment if performed prior to randomization and within 21 days prior to first treatment. Physical examinations performed prior to signing the ICF as part of routine clinical care may be used as baseline assessment, provided it is completed within the indicated time window and the investigator documents there is no change.

Study procedures related to efficacy, safety, sample collection, and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Efficacy Assessments at Baseline and during Study Treatment

Patients may be enrolled in the study with measurable or nonmeasurable but evaluable disease based on RECIST v.1.1 (Attachment 7).

Within 21 days prior to first treatment, baseline tumor measurements will be performed on each patient. Computed tomography scans, including spiral CT scan, 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 scan.

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 scan (with I.V. and oral contrast). A PET scan alone or as part of a PET-CT scan may be performed for additional analyses but cannot be used to assess response according to RECIST v.1.1.

Except when deemed unfeasible in the opinion of the investigator due to patient's clinical status, imaging studies and tumor assessments will be performed as scheduled every 6 weeks (±7 days) as calculated from randomization for the first year; thereafter, every 9 weeks (±7 days), even if therapy is delayed. The method of assessment used at baseline must be used consistently for post-baseline tumor assessments and will be repeated according to the protocol schedule.

Since 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, copies of all scans will be collected throughout the study and stored centrally by a coordinating vendor designated by Lilly.

10.1.2. Efficacy Assessments during the Study Period Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted as described in the Study Schedule (Attachment 1).

For those patients who discontinue study treatment of Part A without radiographically documented PD, the investigative sites will continue to evaluate tumor response according to the protocol schedule by the same method used at baseline and throughout the study until radiographically documented PD, death, start of Part B, or study completion, except when not feasible in the opinion of the investigator due to patient's clinical status. After the patient has documented disease progression, radiologic assessments are no longer required and the patient will be followed up every 12 weeks (±14 days) until the patient's death or study completion, whichever is earlier (see Attachment 1).

10.1.3. Primary Efficacy Measure

The PFS time is measured from the date of randomization to the date of radiographic documentation of progression (as defined by RECIST v.1.1) or the date of death due to any cause, whichever is earlier during Part A. If a patient is not known to have died or have radiographically documented progression as of the data cutoff date for the primary endpoint analysis, the PFS time will be censored at the last adequate tumor assessment date. If the Part B treatment or other postdiscontinuation therapy was started before observing PD, the PFS will be censored at the date of last adequate tumor assessment before staring the Part B treatment or other postdiscontinuation therapy. Further details of censoring rules will be provided in the statistical analysis plan (SAP).

A sensitivity analysis will include patients who have had symptomatic progression as progression events. Additional sensitivity analyses for PFS will be performed with respect to various censoring rules and will be specified in the SAP.

10.1.4. Secondary Efficacy Measures

Table JVCW.10.1 lists the secondary efficacy measures that will be collected at the times shown in the Study Schedule (Attachment 1).

Table JVCW.10.1.   Secondary Efficacy Endpoints

Endpoint	Definition
PFS2	The time from the date of randomization to the date of first tumor assessment observing PD after the start of second-line therapy using the last tumor assessment before starting the second-line therapy (RAM+PTX) as the baseline assessment, or death. If the second-line therapy was not started, the OS will be substituted for PFS2. If the patient was alive at the cutoff for analysis (or was lost to follow-up) and a second disease progression has not been observed, PFS2 data will be censored on the last date the patient was known to be alive. If a postdiscontinuation therapy was started before observing PD after the start of second-line therapy, the PFS2 will be censored at the date of the last adequate tumor assessment before staring the postdiscontinuation therapy. Further details of censoring rules will be provided in the SAP.
Overall Survival	The time from the date of randomization to the date of death from any cause. If the patient was alive at the cutoff for analysis (or was lost to follow-up), OS data will be censored for analysis on the last date the patient was known to be alive.
Objective Response Rate	The proportion of randomized patients achieving a best overall response of CR or PR in Part A.
Disease Control Rate	The proportion of randomized patients achieving a best overall response of CR, PR, or SD in Part A.

Abbreviations: CR = complete response; OS = overall survival; PD = progressive disease; PFS2 = progression-free survival 2; PR = partial response; PS = performance status; PTX = paclitaxel; RAM = ramucirumab; SAP = statistical analysis plan; SD = stable disease.

10.1.5. Exploratory Efficacy Measures

The following exploratory efficacy measures for Part B (Table JVCW.10.2) will be collected at the times shown in the Study Schedule (Attachment 1).

Table JVCW.10.2.   Exploratory Efficacy Endpoints for Part B

Endpoint	Definition
PFS2-1	The time from the last tumor assessment date before starting second-line therapy (RAM+PTX) to the first tumor assessment date observing PD, using the last tumor assessment before starting the second-line therapy as the baseline assessment, or date of death. Further details of censoring rules will be provided in the SAP.
OS2	The time from the start date of second-line therapy (RAM+PTX) to the date of death from any cause.
ORR2	The proportion of patients receiving any quantity of study treatment for Part B achieving a best overall response of CR or PR in Part B.
DCR2	The proportion of patients receiving any quantity of study treatment for Part B achieving a best overall response of CR, PR, or SD in Part B.

Abbreviations: CR = complete response; DCR2 = disease control rate of second-line therapy; ORR2 = objective response rate of second-line therapy; OS2 = overall survival of second-line therapy; PD = progressive disease; PFS2-1 = progression-free survival of second-line therapy; PR = partial response; PTX = paclitaxel; RAM = ramucirumab; SAP = statistical analysis plan; SD = stable disease.

10.2. Safety Evaluations

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, 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 Study Schedule (Attachment 1). Table JVCW.10.3 presents a summary of AE and SAE reporting guidelines. Table JVCW.10.3 also shows which database or system is used to store AE and SAE data.

Table JVCW.10.3.   Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System[a]
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs	x	
	SAEs related to protocol procedures	x	x
Treatment period	All AEs	x	
	All SAEs	x	x
Short-term safety follow-up (postdiscontinuation follow-up)	All AEs	x	
	All SAEs	x	x
Long-term follow-up (postdiscontinuation follow-up)	All SAEs related to protocol procedures or any component of study treatment	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 (ie, no longer receiving study treatment and no longer in follow-up)	All SAEs related to protocol procedures or any component of study treatment of which the investigator becomes aware		x

Abbreviations: AE = adverse event; SAE = serious adverse event.

a   Site staff do not need to enter data into the Lilly Safety System.

10.2.1. 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.

Cases of pregnancy that occur during maternal or paternal exposures to study treatment up to 24 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. Preexisting conditions should not be reported as AEs unless they worsen during the study.

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

In addition, all AEs occurring after the patient receives the first dose of IP must be reported to Lilly or its designee via eCRF. See Table JVCW.10.3 for the AE and SAE reporting guidelines during and after continued access.

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

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
- **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/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.

The NCI-CTCAE v. 4.03 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 terminology within the NCI-CTCAE v. 4.03 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event (grade as mild [Grade 1], moderate [Grade 2], severe [Grade 3], very severe/life-threatening [Grade 4], or death [Grade 5]).

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

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 eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.2.1.1. Interstitial Lung Disease

For ILD and suspected ILD cases being diagnosed after starting the study drug (Cycle 1, Day 1), external specialists may evaluate its related examination results, such as image data. The investigator should provide the test results, including imaging examination and pathological examination, upon request of the sponsor.

10.2.1.2. 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 (ie, 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 informed consent and has received IP. If a patient experiences an SAE after signing informed consent, but prior to receiving IP, 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 **serious** AE within 24 hours of investigator awareness of the event via a sponsor-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. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the 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 the sponsor, 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 the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.2.1.3. 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 the study treatment or study procedure. US 21 CFR 312.32 and EU 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.

10.2.2. Other Safety Measures

10.2.2.1. Electrocardiograms

For each patient, a single 12-lead digital ECG will be obtained according to the Study Schedule (Attachment 1). The patient must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms 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 [QTc] 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.

10.2.3. Safety Monitoring

The Lilly CRP, CRS, or designee will monitor safety data throughout the course of the study.

Representatives from Lilly Global Patient Safety (GPS) will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures. The Lilly CRP or CRS will, as is appropriate, consult with the functionally independent GPS therapeutic area physician and periodically review:

- Trends in safety data
- Laboratory analytes
- AEs
- If a patient experiences elevated ALT >5x ULN and elevated total bilirubin >2x ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT >3x ULN, monitoring should be triggered at ALT >2x baseline (see Attachment 5).
- 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, CRS, or designee regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 5).

Refer to the latest version of the ramucirumab IB for information regarding the agent's reasonably anticipated AEs/SAEs expected in the study population.

10.2.4. Complaint Handling

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

Complaints related to unblinded comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or its designee will be reported.

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.

10.3. Sample Collection and Testing

Attachment 1 lists the schedule of events in this study.

Attachment 3 lists the PK, pharmacodynamics, immunogenicity, and translational research sampling schedule.

Attachment 4 lists the specific laboratory tests that will be performed in this study.

Attachment 5 lists tests that may be obtained in the event of a treatment-emergent hepatic abnormality.

10.3.1. 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.

For patient and study site convenience and safety, randomization and treatment decisions will be based upon results of tests performed locally (Attachment 4). All tests which require central laboratory processing must still be collected and submitted to the central laboratory.

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.

10.3.2. Stored Samples for Translational Research

Patient participation in the translational research portion of the study is mandatory, unless restricted by local regulations or ERBs. As part of the sponsor's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study may analyze biomarkers relevant to ramucirumab, angiogenesis, VEGF pathway, S-1, oxaliplatin, paclitaxel, and/or gastric and GEJ adenocarcinoma. The study will analyze the clinical correlation between biomarkers and clinical outcome.

The following samples are required for biomarker research:

- Whole blood samples (within 14 days prior to initial infusion of ramucirumab/placebo on Day 1 Cycle 1 preferred, otherwise later during the trial is acceptable)
- Plasma samples

The following samples are optional for participation in this study:

- Archived tumor tissue

10.3.2.1. Whole Blood Sample for Deoxyribonucleic Acid Collection

A blood sample will be collected for pharmacogenetic analysis as specified in Attachment 3.

Pharmacogenetics is a branch of science that uses genetic information to better understand why people respond differently to drugs. It is for this reason, in the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker sample may be genotyped and analysis may be performed to evaluate a genetic association with response to ramucirumab and/or S-1, oxaliplatin, and paclitaxel. Samples will also be used to investigate genetic variants thought to play a role in gastric or GEJ adenocarcinoma (and associated cancers) and/or cancer related conditions to aid in understanding variability in response to the study drugs. These samples will not be used for broad exploratory unspecified disease or population genetic analysis.

Examples of genetic biomarkers that may influence clinical efficacy observed in Study JVCW include genes in the angiogenesis pathway (eg, VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGFR-1, VEGFR-2, and VEGFR-3). New information is likely to develop during the course of this study or by the time translational research assessments are performed. This will result in additional biomarkers to be studied that will be related to gastric/GEJ adenocarcinoma (or cancer related conditions), the mechanism of ramucirumab, or angiogenesis, and may also be used for related research methods.

The samples will be coded with the patient number and stored for up to a maximum of 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from it can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study treatment. Pharmacogenetic data will not be provided back to the investigator or the patient except where required by local law.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. The best technology available for assessing the genes of interest will be utilized at the time this research is conducted. However, regardless of the technology utilized, genotyping data generated will be used only for the specific research scope described here and will not be used for conducting unspecified disease or population genetic research either now or in the future.

10.3.2.2. Tumor Tissue Samples

The collection of archived tumor samples for biomarker research is optional for this trial. If collected, this sample should be obtained at the time specified in the sampling schedule (see Attachment 3) where local regulations and ERBs allow. Due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying archival tissue may also be requested (de-identified and translated).

Samples will be used for research on biomarkers relevant to ramucirumab, angiogenesis, VEGF pathway, S-1, oxaliplatin, paclitaxel, and/or gastric and GEJ adenocarcinoma, and/or research method or in validating diagnostic tools or assay(s) related to cancer.

Examples of biomarkers may include the VEGF pathway (VEGF Receptor 2 expression), disease-associated mutations (MET), copy number alterations (VEGF-A and VEGF Receptor 2)

and fusion proteins. New information is likely to develop during the course of this study or by the time the translational research assessments are performed. This will result in additional biomarkers to be studied that are relevant to ramucirumab, angiogenesis, VEGF pathway, S-1, oxaliplatin, paclitaxel, and/or gastric and GEJ adenocarcinoma and/or research methods or in validating diagnostic tools or assay(s) related to cancer.

Mutation profiling, copy number variability, gene expression, and/or immunohistochemistry may be performed on these tissue samples to detect these biomarkers and assess potential associations between these biomarkers and clinical outcomes; however, technologies are expected to improve within the storage period. Regardless of technology utilized data generated will only be used for the specific research scope described here.

Pretreatment formalin-fixed paraffin-embedded tumor tissue obtained from the primary tumor or metastatic site should be provided as a whole block or unstained slides (at least 20 slides). All tissue samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

10.3.2.3. Plasma Samples

Plasma samples for non-pharmacogenetic biomarker research are required from all patients in this study, unless restricted per local regulations or ERBs. Plasma will be collected at the times specified in the sampling schedule (see Attachment 3).

Samples will be used for research on the drug target, disease process, pathways associated with cancer, angiogenesis, mechanism of action of ramucirumab, S-1, oxaliplatin, and/or paclitaxel, variable response to study drug (including the evaluation of adverse events or differences in efficacy), and/or research method or in validating diagnostic tools or assay(s) related to cancer.

Some examples of pharmacodynamics and/or circulating biomarkers may include VEGF-A, VEGF-C, VEGF-D, placental growth factor (PlGF), soluble vascular endothelial cell growth factor (sVEGF) Receptor 1, sVEGF Receptor 2, and sVEGF Receptor 3. New information is likely to develop during the course of this study or by the time translational research assessments are performed. This will result in additional biomarkers to be studied that will be related to gastric/GEJ adenocarcinoma (or cancer-related conditions), the mechanism of ramucirumab, and angiogenesis, and may also be used for related research methods.

All biomarker samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory

questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

10.3.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against ramucirumab at baseline (BEFORE the first infusion of ramucirumab on Cycle 1 Day 1 of treatment), at specified time points during the study, and in the event of an IRR, as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event (see 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.

To interpret the results of immunogenicity, the concentration of ramucirumab in the blood will also be measured at the same time points (see Attachment 3).

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

10.3.4. Samples for Drug Concentration Measurements (Pharmacokinetics)

Blood samples will be collected from all study patients to assess serum ramucirumab concentrations as specified in Attachment 3. Instructions and supplies for the collection, handling, and shipping of samples will be provided by either the sponsor or the central laboratory.

In the event of an IRR, every attempt should be made to collect blood samples for determination of anti-ramucirumab antibody and serum ramucirumab concentration at those given time points, as described in Attachment 3.

Serum ramucirumab concentrations will be analyzed at a laboratory designated by the sponsor using a validated method.

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

10.4. Appropriateness of Measurements

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

LY3009806

11. 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/third-party organization (TPO) start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, 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 eCRF 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.

11.1. Data Capture System

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

Case report form data will be encoded and stored in a clinical trial database. Validated data will subsequently be transferred to the Lilly data warehouse, using standard Lilly file transfer processes. Any data handled by the sponsor internally will be managed by the sponsor and stored electronically in the sponsor's data warehouse.

Data managed by a central vendor 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.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary objective of this study is to compare PFS of ramucirumab in combination with S-1 and oxaliplatin versus placebo in combination with S-1 and oxaliplatin as first-line treatment in patients with metastatic gastric or GEJ adenocarcinoma.

The study will enroll approximately 190 patients in 1:1 randomization and the primary endpoint analysis will be performed 6 months after observing 111 PFS events. The expected number of PFS events at this time point is 136 and the probability of having a 2-sided p-value of less than 0.2 (correspond to 1-sided 0.1) using a log-rank test in terms of PFS would be approximately 85%, assuming the recruitment rate of 8 patients per month, the HR of 0.67 (median 6 months vs. 9 months) and approximately 10% of enrolled patients would be censored before the data cut-off. The probability of having a 2-sided p-value of less than 0.2 with 111 events under the same assumption would be 80%.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

All CIs will be given at a 2-sided 80% level, 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. Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the SAP. 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.

If study data violate key statistical assumptions of an analysis method, alternative statistical methods may be used.

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

12.2.1.1. Analysis Populations

The following populations will be defined for this study:

Full Analysis Set (FAS): will include all randomized patients receiving any quantity of study treatment for Part A and grouped according to the treatment the patients were assigned. This population will be used for all baseline and efficacy analyses.

Per-Protocol Set (PPS): will include all patients who are randomized and received at least 1 cycle of study treatment, and do not have any major protocol violations that could potentially affect the efficacy conclusions of the study. This population will be defined in detail in the

SAP prior to database lock, and will be used for sensitivity analyses of PFS, PFS2, and OS; other efficacy endpoints may also be analyzed.

Safety population (SP): will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the actual study treatment a patient has received, regardless of the treatment arm to which he or she was randomized. The safety population will be used for all dosing/exposure, AEs, laboratory tests, and vital sign analyses.

Full Analysis Set for Part B (FAS2): will include all patients receiving any quantity of study treatment for Part B and grouped according to the treatment the patients were assigned at randomization. This population will be used for exploratory analyses of PFS2-1, ORR2, DCR2, and OS2.

Safety population for Part B study treatment (SP2): will include all patients who received any quantity of study treatment for Part B. The safety evaluation will be performed based on the actual study treatment a patient has received, regardless of the treatment arm to which he or she was randomized. This population will be used for all dosing/exposure, AEs, laboratory tests, and vital sign analyses for Part B.

Safety population for Part B ramucirumab (SP3): will include all patients who received any quantity of ramucirumab for Part B. The safety evaluation will be performed based on the actual ramucirumab treatment a patient received, regardless of the treatment arm to which he or she was randomized. This population will be used for all dosing/exposure, AEs, laboratory tests, and vital sign analyses for Part B.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. This will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as the 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.

12.2.3. 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.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety populations.

12.2.4.1. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name for FAS and FAS2.

12.2.5. Treatment Compliance

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

12.2.6. Primary Outcome and Methodology

Progression-free survival time is defined as the time from randomization until the first radiographic documentation of progression as defined by RECIST v.1.1, or death due to any cause, whichever is earlier. Stratification will be based on the same stratification factors included in the randomization.

The analysis of PFS will be based on stratified log-rank test and estimation of HR using stratified Cox regression model, stratified by randomization strata (eCRF). Stratified log-rank test's p-value of less than 0.2 from 2-sided test with 136 events for the PFS (approximately HR ≤0.8), would be interpreted that ramucirumab + oxaliplatin + S-1 is a promising regimen as a first-line therapy for patients with advanced gastric or GEJ adenocarcinoma who have not received prior first-line chemotherapy. Progression-free survival curves, medians with 80% CIs, and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method.

12.2.7. Other Analyses of Efficacy

Progression-free survival

The following sensitivity analyses will be performed for PFS:

- unstratified log-rank test and Cox models

- stratified log-rank test and Cox models, stratified by strata collected in IWRS

- analysis including both radiographic and symptomatic progressions as PFS events

- analysis for the per-protocol set

- sensitivity analysis for various PFS censoring rules (eg, post-discontinuation systemic anticancer therapy, missing 2 or more tumor assessments prior to PD/death; more details will be specified in the SAP)

- Univariate and multivariate Cox regression model will be used to explore potential prognostic and/or predictive factors

- Additional sensitivity analyses may be specified in the SAP.

Overall survival

- The analysis of OS will be based on a stratified log-rank test and estimation of HR using stratified Cox regression model, stratified by randomization strata (eCRF).

- OS survival curves, medians with 80% CIs, and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method.

- OS will be analyzed for FAS.

- The following sensitivity analyses may be performed for OS:

    o Unstratified log-rank test and Cox models

    o stratified log-rank test and Cox models, stratified by strata collected in IWRS

    o analysis for the per-protocol set

    o Univariate and multivariate Cox regression model will be used to explore potential prognostic and/or predictive factors.

    o Additional sensitivity analyses may be specified in the SAP.

Progression-free survival 2

- The analysis of PFS2 will be based on stratified log-rank test and estimation of HR using stratified Cox regression model, stratified by randomization strata (IWRS). The PFS2 median with 80% CI and survival curves for each treatment group will be estimated using Kaplan-Meier method.

- An additional sensitivity analysis may be explored in which an event is defined as discontinuation of second-line treatment, second disease progression, or death from any cause, whichever occurs first. Other sensitivity analyses may be specified in the SAP.

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 patients who achieve a best overall response of CR or PR, divided by the total number of patients randomized to the corresponding treatment group (FAS). 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 are considered as nonresponders and are included in the denominator when calculating the response rate. The ORR with 80% CI observed in each treatment group will be summarized and compared using the Cochran-Mantel-Haenszel test adjusting for the randomization strata (eCRF).

Exploratory efficacy analyses for Part B

- For ORR2, DCR2, PFS2-1, and OS2 (time from the start date of second-line therapy to the date of death), analyses will be conducted on FAS2.

- ORR2 and DCR2 will be estimated together with 80% CIs for each treatment arm and in total.

- For PFS2-1 and OS2, the Kaplan-Meier method will be used to estimate the survival curves for each treatment arm and in total.

- ORR2 and DCR2 use the last tumor assessment before starting second-line therapy as the baseline assessment.

- PFS2-1 is defined as the time from the last tumor assessment date before starting second-line therapy to the first tumor assessment date observing PD, using the last tumor assessment before starting the second-line therapy as the baseline assessment, or date of death.

Additional exploratory analyses may be performed as deemed appropriate.

12.2.8. *Pharmacokinetic and Immunogenicity Analyses*

Serum ramucirumab concentrations prior to infusion (minimum concentration [C_{min}]) will be summarized using descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate. Relationships between ramucirumab exposure and measures of efficacy and safety may be explored if deemed appropriate. Details will be described in the SAP.

Immunogenicity incidence will be tabulated, and correlation of immunogenicity to ramucirumab drug level, activity, and safety will be assessed, as appropriate.

12.2.9. *Safety Analyses*

Safety summaries will be provided separately for Part A and Part B. Safety listings will include the safety data through Part A and Part B. Safety summaries for Part A and safety listings will be based on the SP. Safety summaries for Part B will be based on the SP2 and/or SP3. Safety populations are defined in Section 12.2.1.1.

Safety summaries will include:

- Adverse events will be summarized by MedDRA System Organ Class/preferred term, classified from verbatim terms. The incidence and percentage of patients with at least 1 occurrence of a preferred term will be included, according to the most severe NCI-CTCAE v. 4.03 grade. Causality (relationship to study drug), action taken, and outcome will be summarized separately. Duration of AE will be determined and included in the listings.

- Study drug exposure will be summarized for each treatment arm with the following variables: number of infusion (except for S-1), number of cycles, duration of therapy, cumulative dose, dose intensity, and relative dose intensity.

- Laboratory results will be classified according to NCI-CTCAE v. 4.03. Incidence of laboratory abnormalities will be summarized.

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

Further safety analyses may be performed as deemed appropriate.

12.2.10. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics (eg, prognostic significance) and will be used to analyze any difference in treatment effects.

12.2.11. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. 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. 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 IP.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the 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 study site's 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

13.3. 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 (CIOMS) International Ethical Guidelines
- ICH GCP Guideline (E6)
- applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a TPO.

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.

LY3009806

13.3.1. Investigator Information

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

13.3.2. Protocol Signatures

The sponsor'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.

13.3.3. 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.

The investigator chosen by Lilly or designee will serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will sign/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.

14. References

Amini A, Moghaddam SM, Morris DL, Pourgholami MH. The critical role of vascular endothelial growth factor in tumor angiogenesis. *Curr Cancer Drug Targets*. 2012;12(1):23-43.

Andersen S, Donnem T, Al-Saad S, Al-Shibli K, Busund LT, Bremnes RM. Angiogenic markers show high prognostic impact on survival in marginally operable non-small cell lung cancer patients treated with adjuvant radiotherapy. *J Thorac Oncol*. 2009;4(4):463-471.

[ASCO] American Society of Clinical Oncology, Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Morrow GR, Chinnery LW, Chesney MJ, Gralla RJ, Grunberg SM. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006 [published correction appears in *J Clin Oncol*. 2006;24(33):5341-5342]. *J Clin Oncol*. 2006;24(18):2932-2947.

Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Ruschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA); a phase 3, open-label, randomised controlled trial [published correction appears in *Lancet*. 2010;376(9749):1302]. *Lancet*. 2010;376(9742):687-697.

Benson AB 3rd, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA Jr, McCallum R, Mitchell EP, O'Dorisio TM, Vokes EE, Wadler S. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol*. 2004;22(14):2918-2926.

Cockcroft DW, Gault MD. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

Crawford J, Caserta C, Roila F; ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO recommendations for the applications. *Ann Oncol*. 2009;20(suppl 4):iv162-iv165.

CYRAMZA [package insert]. Indianapolis, IN: Eli Lilly and Company; 2014.

Doi T, Boku N, Kato K, Komatsu Y, Yamaguchi K, Muro K, Hamamoto Y, Sato A, Koizumi W, Mizunuma N, Takiuchi H. Phase I/II study of capecitabine plus oxaliplatin (XELOX) plus bevacizumab as first-line therapy in Japanese patients with metastatic colorectal cancer. *Jpn J Clin Oncol*. 2010;40(10):913-920.

Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

Enzinger PC, Fidias P, Meyerhardt J, Stuart K, Fuchs C, Huberman M, Goldstein R, Attawia M, Lawrence C, Zhu AX. Phase II study of bevacizumab and docetaxel in metastatic esophageal and gastric cancer. In: proceedings from the the American Society for Clinical Oncology Gastrointestinal Symposium; January 26-28, 2006; San Francisco, CA. Abstract 68.

[FDA] US Food and Drug Administration. Information on Erythropoiesis Stimulating Agents. Available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders /ucm109375.htm. Accessed July 27, 2014.

Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, dos Santos LV, Aprile G, Ferry DR, Melichar B, Tehfe M, Topuzov E, Zalcberg JR, Chau I, Campbell W, Sivanandan C, Pikiel J, Koshiji M, Hsu Y, Liepa AM, Gao L, Schwartz JD, Tabernero J; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383(9911):31-39.

Garg RK. Posterior leukoencephalopathy syndrome. *Postgrad Med J.* 2001;77(903):24-28.

Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, Svenson C, Enander LK, Linne T, Sellsrom H, Heuman R. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol.* 1997;8(2):163-168.

Goldman J, Rutkowski JM, Shields JD, Pasquier MC, Cui Y, Schmokel HG, Willey S, Hicklin DJ, Pytowski B, Swartz MA. Cooperative and redundant roles of VEGFR-2 and VEGFR-3 signaling in adult lymphangiogenesis [published correction appears in *FASEB J.* 2007;21(8):1942]. *FASEB J.* 2007;21(4):1003-1012.

Goto M. Result of phase III study of S-1 plus cisplatin versus S-1 plus oxaliplatin for advanced or recurrence gastric cancer and development to personalized medicine. In: proceedings from the Japanese Gastric Cancer Association. March 20-22, 2014. Yokohama, Japan. Abstract # PD7-7.

Gralla RJ, Roila F, Tonato M, Herrstedt J. Multinational Association of Supportive Care in Cancer - Consensus Conference on Antiemetic Therapy, Latest Update: January 2013. Available at: http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_english_2014.pdf. Accessed May 19, 2015.

Higuchi K, Koizumi W, Yamada Y, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, Nishina T, Amagai K, Chin K, Niwa Y, Negoro Y, Imamura H, Tsuda M, Yasui H, Fujii H, Yamaguchi K, Yasui H, Hamada C, Hyodo I. Randomized phase III study of S-1 plus oxaliplatin versus S-1 plus cisplatin for first-line treatment of advanced gastric cancer. *J Clin Oncol.* 2013;31(suppl 4). Abstract 60.

Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, Pessin MS, Lamy C, Mas JL, Caplan LR. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med.* 1996;334(8):494-500.

[IARC] International Agency for Research on Cancer. Globocan 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed October 16, 2014.

Jantus-Lewintre E, Sanmartín E, Sirera R, Blasco A, Sanchez JJ, Taron M, Rosell R, Camps C. Combined VEGF-A and VEGFR-2 concentrations in plasma: diagnostic and prognostic implications in patients with advanced NSCLC. *Lung Cancer.* 2011;74(2):326-331.

Japan Ministry of Health, Labour and Welfare. Vital statistics. Available at: http://ganjoho.jp/professional/statistics/statistics.html#incidence. Accessed October 21, 2014.

[JGCA] Japan Gastric Cancer Association. Treatment Guideline for Gastric Cancer. 3rd ed. Tokyo: KANEHARA & Co. ltd; 2010.

[JGCA] Japan Gastric Cancer Association. Expansion of oxaliplatin into the indication for treatment of advanced and metastatic gastric cancer. Available at: http://www.jgca.jp/pdf/Oxaliplatin201408_2.pdf. Accessed December 3, 2014.

Jimenez X, Lu D, Brennan L, Persaud K, Liu M, Miao H, Witte L, Zhu Z. A recombinant, fully human, bispecific antibody neutralizes the biological activities mediated by both vascular endothelial growth factor receptors 2 and 3. *Mol Cancer Ther.* 2005;4(3):427-434.

Jung YD, Mansfield PF, Akagi M, Takeda A, Liu W, Bucana CD, Hicklin DJ, Ellis LM. Effects of combination anti-vascular endothelial growth factor receptor and anti-epidermal growth factor receptor therapies on the growth of gastric cancer in a nude mouse model. *Eur J Cancer.* 2002;38(8):1133-1140.

Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol.* 2008;9(3):215-221.

Koizumi W, Takiuchi H, Yamada Y, Boku N, Fuse N, Muro K, Komatsu Y, Tsuburaya A. Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study). *Ann Oncol.* 2010;21(5):1001-1005.

Lee JL, Ryu MH, Chang HM, Kim TW, Yook JH, Oh ST, Kim BS, Kim M, Chun YJ, Lee JS, Kang YK. A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy. *Cancer Chemother Pharmacol.* 2008;61(4):631-637.

Lu D, Shen J, Vil MD, Zhang H, Jiminez X, Bohlen P, Witte L, Zhu Z. Tailoring in vitro selection for a picomolar affinity human antibody directed against vascular endothelial growth factor receptor 2 for enhanced neutralizing activity. *J Biol Chem.* 2003;278(44):43496-43507.

Miao HQ, Hu K, Jimenez X, Navarro E, Zhang H, Lu D, Ludwig DL, Balderes P, Zhu Z. Potent neutralization of VEGF biological activities with a fully human antibody Fab fragment directed against VEGF receptor 2. *Biochem Biophys Res Commun.* 2006;345(1):438-445.

Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer.* 1993;72(1):37-41.

NCCN Clinical Practice Guidelines in Oncology. Gastric Cancer. Version 1.2014. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed October 16, 2014.

Oh SY, Kwon HC, Kim SH, Lee S, Lee JH, Graves CA, Camphausen K, Kim HJ. Prognostic significance of serum levels of vascular endothelial growth factor and insulin-like growth factor-1 in advanced gastric cancer patients treated with FOLFOX chemotherapy. *Chemotherapy.* 2013;58(6):426-434.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol*. 1982;5(6):649-655.

[PMDA] Pharmaceuticals and Medical Devices Agency. TS-1 combination OD tablet. Available at: http://www.info.pmda.go.jp/downfiles/ph/PDF/400107_4229101F1026_1_03.pdf. Accessed October 27, 2014.

Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer*. 1995;71(3):587-591.

Report of Hospital-Based Cancer Registry. Available at: http://ganjoho.jp/data/professional/statistics/hosp_c_registry/2012_report.pdf. Accessed October 16, 2014.

Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, Bennett CL, Bohlius J, Evanchuk D, Goode MJ, Jakubowski AA, Regan DH, Somerfield MR; American Society of Clinical Oncology; American Society of Hematology. American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update on the use of epoetin and darbepoetin in adult patients with cancer. *J Clin Oncol*. 2010;28(33):4996-5010.

Roy H, Bhardwaj S, Yla-Herttuala S. Biology of vascular endothelial growth factors. *FEBS Lett*. 2006;580(12):2879-2887.

Sasako M, Inoue M, Lin JT, Khor C, Yang HK, Ohtsu A. Gastric Cancer Working Group report. *Jpn J Clin Oncol*. 2010;40(suppl 1):i28-i37.

Seto T, Higashiyama M, Funai H, Imamura F, Uematsu K, Seki N, Eguchi K, Yamanaka T, Ichinose Y. Prognostic value of expression of vascular endothelial growth factor and its flt-1 and KDR receptors in stage I non-small-cell lung cancer. *Lung Cancer*. 2006;53(1):91-96.

Shah MA, Ramanathan RK, Ilson DH, Levnor A, D'Adamo D, O'Reilly E, Tse A, Trocola R, Schwartz L, Capanu M, Schwartz GK, Kelsen DP. Multicenter phase II study of irinotecan, cisplatin and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol*. 2006;24(33):5201-5206.

Shen L, Shan YS, Hu HM, Price TJ, Sirohi B, Yeh KH, Yang YH, Sano T, Yang HK, Zhang X, Park SR, Fujii M, Kang YK, Chen LT. Management of gastric cancer in Asia: resource-stratified guidelines. *Lancet Oncol*. 2013;14(12):e535-547.

Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC. Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol*. 2006;24(19):3187-3205.

Stott VL, Hurrell MA, Anderson TJ. Reversible posterior leukoencephalopathy syndrome: a misnomer reviewed. *Intern Med*. 2005;35(2):83-90.

Taiwan Cancer Registry Annual Report 2012. Available at: http://www.hpa.gov.tw/BHPNet/Web/Service/FileCount.aspx?file=StatisticsFile&StatisticsFile=201504290915220898&StatisticsFileName=101%e5%b9%b4%e7%99%8c%e7%97%87%e7%99%bb%e8%a8%98%e5%b9%b4%e5%a0%b1.pdf. Accessed: July 15, 2015.

Tajima Y, Isonishi K, Kashiwaba T, Tashiro K. Two similar cases of encephalopathy, possibly a reversible posterior leukoencephalopathy syndrome: serial findings of magnetic resonance imaging, SPECT, and angiography. *Intern Med*. 1999;38(1):54-58.

Tvorogov D, Anisimov A, Zheng W, Leppanen VM, Tammela T, Laurinavicius S, Holnthoner W, Helotera H, Holopainen T, Jeltsch M, Kalkkinen N, Lankinen H, Ojala PM, Alitalo K. Effective suppression of vascular network formation by combination of antibodies blocking VEGFR ligand binding and receptor dimerization. *Cancer Cell*. 2010;18(6):630-640.

Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA; V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 study group. *J Clin Oncol*. 2006;24(31):4991-4997.

Vanhoefer U, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Cutsem E, Planker M, Santos JG, Piedbois P, Paillot B, Bodenstein H, Schmoll HJ, Bleiberg H, Nordlinger B, Couvreur ML, Baron B, Wils JA. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer. A trial of the European Organization for Research and Treatment of Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol*. 2000;18(14):2648-2657.

Wilke H, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim T-Y, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15(11):1224-1235.

Xie LX, Zhai TT, Yang LP, Yang E, Zhang XH, Chen JY, Zhang H. Lymphangiogenesis and prognostic significance of vascular endothelial growth factor C in gastro-oesophageal junction adenocarcinoma. *Int J Exp Pathol*. 2013;94(1):39-46.

Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, Nishina T, Amagai K, Chin K, Niwa Y, Tsuji A, Imamura H, Tsuda M, Yasui H, Fujii H, Yamaguchi K, Yasui H, Hironaka S, Shimada K, Miwa H, Hamada C, Hyodo I. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. *Ann Oncol*. 2015;26(1):141-148.

Yamada Y, Takahari D, Matsumoto H, Baba H, Nakamura M, Yoshida K, Yoshida M, Iwamoto S, Shimada K, Komatsu Y, Sasaki Y, Satoh T, Takahashi K, Mishima H, Muro K, Watanabe M, Sakata Y, Morita S, Shimada Y, Sugihara K. Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT): an open-label, non-inferiority, randomised phase 3 trial [published correction appears in *Lancet Oncol*. 2014;15(1):e4]. *Lancet Oncol*. 2013;14(13):1278-1286.

Zhu Z, Hattori K, Zhang H, Jiminez X, Ludwig DL, Dias S, Kussie P, Koo H, Kim HJ, Lu D, Liu M, Tejada R, Friedrich M, Bohlen P, Witte L, Rafii S. Inhibition of human leukemia in an animal model with human antibodies directed against vascular endothelial growth factor receptor 2. Correlation between antibody affinity and biological activity. *Leukemia*. 2003;17(3):604-611.

Attachment 1. Protocol JVCW Study Schedule

Perform procedure as indicated.

Study Schedule, Protocol I4T-JE-JVCW – Part A

Study Procedures	Screening[a]			Cycle 1 (21-day cycle)			Cycle 2-n (21-day cycles)			Pre-treatment Period of Part B[b] (up to 12 weeks)
Relative Day within Cycle	≤21	≤14	≤7	1	8 (+3d)	15	1 (±3d)	8 (+3d)	15	
Visit	000			001			002-XXX			200
Informed consent[c]		X								
HBV[d]		X								
Demography		X								
Medical history		X								
Concomitant medications[e]		X		X	X		X	X		
Toxicity/AE assessment		X		X	X		X	X		
ECOG performance status		X					X			
ECG[f]		X								
TSH, free T4, HgbA1c		X								
Physical exam, weight, and height[g]			X				X			
Vital signs[h]			X	X	X		X	X		
Hematology profile[i]			X		X		X	X		See Schedule for Part B
Coagulation profile[j]			X				X			
Serum chemistry profile[k]			X		X		X	X		
Urinalysis[l]			X		X		X	X		
Pregnancy test[m]			X							
Imaging/tumor assessment[n]	X			X						
PK/Pharmacodynamic /Immunogenicity/ Translational Research	See Sampling Schedule (Attachment 3)									
Ramucirumab/Placebo infusion[o]				X	X		X	X		
S-1 intake[o]				X (d1-d14)			X (d1-d14)			
Oxaliplatin infusion[o]				X			X			

Abbreviations: AE = adverse event; CT = computed tomography; d = day; ECG = electrocardiogram;
ECOG = Eastern Cooperative Oncology Group; HBV = Hepatitis B virus; HgbA1c = hemoglobin A1c; IWRS =
interactive web response system; PD = progressive disease; PK = pharmacokinetics; RECIST = Response
Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone; T4 = thyroxine.

a For screening, data or information collected prior to the date of consent may be used.

b Pre-treatment period for Part B begins the day after the decision is made that the patient will no longer continue
study treatment in Part A. Patients who meet the initiation criteria for Part B can start administration of study
treatment of Part B. Patients who do not meet initiation criteria for Part B within 12 weeks from decision of
study treatment discontinuation of Part A should be discontinued from the study. Patients who will start next
treatment other than Part B treatment or decide not to move to Part B must be followed for 30 days (±7 days)
after the decision is made that the patient will discontinue from the study.

c Written informed consent will be given by each patient prior to undergoing any protocol-specific evaluations.

d Documentation of a negative test result within 24 weeks prior to randomization must be available for HBV.

e Concomitant medications will be recorded, including any taken within 21 days prior to Cycle 1 Day 1.

f More frequent ECGs may be done if clinically indicated.

g Height measurement to be performed during the Screening period of Part A only. Weight to be measured within
3 days prior to treatment at each cycle. If there is a ≥10% change (increase or decrease) in body weight from the
last dose calculation, then dose must be recalculated.

h Vital signs include temperature, pulse rate, and blood pressure and will be obtained immediately prior to and at
the completion of each infusion of ramucirumab/placebo, as well as at the end of the 1-hour observation period
(initial 2 administrations of ramucirumab/placebo only). For subsequent administrations, only blood pressure
and pulse need to be recorded prior to each infusion of ramucirumab/placebo. Other vital signs may be obtained
as clinically indicated. Vital signs can be skipped in cases where only S-1 and/or oxaliplatin are administered.

i Baseline laboratory assessments can be used for dosing for Cycle 1 Day 1. For subsequent visits, laboratory
assessments must be performed within 3 days prior to treatment on Cycle 1 Day 8, and Day 1 and Day 8 of every
subsequent cycle.

j Coagulation should be performed every odd-numbered cycle, unless clinically indicated. Baseline laboratory
assessments can be used for dosing for Cycle 1 Day 1. For subsequent cycles, coagulation must be performed
within 3 days prior to treatment on Day 1 of every odd-numbered cycle.

k Baseline lab assessments can be used for dosing for Cycle 1 Day 1. For subsequent cycles, lab assessments must
be performed within 3 days prior to treatment on Cycle 1 Day 8, and Day 1 and Day 8 of every subsequent cycle.

l Routine dipstick measurements at baseline can be used for dosing for Cycle 1 Day 1. For subsequent cycles,
routine dipstick measurements must be performed within 3 days prior to treatment on Cycle 1 Day 8, and Day 1
and Day 8 of every subsequent cycle. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour
urine collection or urine protein/creatinine ratio must be obtained to assess protein. Test of urinalysis can be
skipped if ramucirumab/placebo is not administered due to treatment delay/omission.

m The urine or serum pregnancy test for women of childbearing potential must be performed within 7 days prior to
first dose of study treatment.

n Baseline radiological tumor assessment of the chest, abdomen, and pelvis per RECIST v.1.1 should be performed
within 21 days prior to first treatment. Magnetic resonance imaging may be used if CT scan is contraindicated.
Radiologic assessments obtained previously as part of routine clinical care may be used as the baseline
assessment if performed within 21 days prior to first treatment and meeting protocol specifications. The method
used at baseline must be used consistently for postbaseline tumor assessments. Tumor assessment to be
performed every 6 weeks (±7 days) from randomization for the first year, and every 9 weeks ±7 days thereafter
even if treatment is delayed. Patients who discontinue for reasons other than radiographically documented PD
will continue tumor assessment every 6 weeks (±7 days) as calculated from randomization until radiographically
documented PD, death, start of Part B, or study completion except when not feasible in the opinion of the
investigator due to patient's clinical status.

o First treatment will be administered within 7 days following randomization. Enter dispensing information into IWRS at each treatment administration.

Study Schedule, Protocol I4T-JE-JVCW – Part B

Study Procedures		Pre-treatment Period of Part B (up to 12 weeks)	Cycle 1 (28-day cycle)				Cycle 2-n (28-day cycles)				Short term Safety Follow-up[a] (30 ±7d)	Long-term Follow-Up (Every 12 weeks ±2 weeks)
Relative Day within Cycle		≤7	1	8 (+3d)	15 (+3d)	22	1 (±3d)	8 (+3d)	15 (+3d)	22		
Visit		200	201				202-20X				801	802-80X
Informed consent[b]		X										
Physical exam, weight[c]		X					X				X	
Concomitant medications[d]		X	X	X	X		X	X	X		X	
ECOG performance status		X					X				X	
ECG[e]		X									X	
Vital signs[f]			X		X		X		X		X	
Criteria for Starting Next Cycle	Toxicity/AE assessment	X	X	X	X		X	X	X		X	
	Hematology profile[g]	X		X	X		X	X	X		X	
	Coagulation profile[h]	X					X				X	
	Serum chemistry profile[g]	X		X	X		X	X	X		X	
	Urinalysis[i]	X			X		X		X		X	
TSH, free T4, HgbA1c											X	
Pregnancy test[j]											X	
Imaging/tumor assessment[k]		X	X									
Survival status and postdiscontinuation therapy[l]											X	X
PK/ Pharmacodynamic /Immunogenicity		See Sampling Schedule (Attachment 3)										
Ramucirumab infusion			X		X		X		X			
Paclitaxel infusion			X	X	X		X	X	X			

Abbreviations: AE = adverse event; CT = computed tomography; d = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HBV = Hepatitis B virus; HgbA1c = hemoglobin A1c; OS = overall survival; PD = progressive disease; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone; T4 = thyroxine.

a   Short-term safety follow-up begins the day after the decision is made that the patient will not move to Part B or no longer continue study treatment of Part B and lasts 30 (±7) days. All patients must be followed for 30 (±7) days after the decision of study treatment discontinuation. Patients who will start next treatment before 30 (±7) days after the decision must be followed before starting next treatment. In the event that a patient in the pre-treatment period of Part B does not move to Part B, the patient will begin the short-term safety follow-up period and data or information collected in the pre-treatment period of Part B may be used.

b   Written informed consent will be given by each patient prior to undergoing any protocol-specific evaluations.

c   Weight to be measured within 3 days prior to treatment at each cycle. If there is a ≥10% change (increase or decrease) in body weight from the last dose calculation, then dose must be recalculated.

d   Concomitant medications will be recorded, including any taken during the 30 days after the decision of study treatment discontinuation.

e   More frequent ECGs may be done if clinically indicated.

f   Vital signs, including pulse rate and blood pressure, will be obtained immediately prior to each infusion of ramucirumab.

g   At every visit that includes administration of study medication, blood will be collected for hematology/serum chemistry within 3 days prior to administration of study medication.

h   Coagulation should be performed every odd-numbered cycle, unless clinically indicated. Every test must be performed within 3 days prior to treatment on Day 1 of every odd-numbered cycle.

i   Routine dipstick measurements must be performed within 3 days prior to treatment on Day 1 and Day 15 of every cycle. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection or urine protein/creatinine ratio must be obtained to assess protein. Test of urinalysis can be skipped if ramucirumab is not administered due to treatment delay/omission.

j   The urine or serum test in women of childbearing potential must be performed 30 days (±7 days) after the decision of study treatment discontinuation.

k   Baseline radiological tumor assessment of the chest, abdomen, and pelvis per RECIST v.1.1 should be performed within 28 days prior to first treatment of Part B. The assessment, which is performed in Part A and 28 days prior to first treatment of Part B, can be used as the baseline assessment of Part B. Magnetic resonance imaging may be used if CT scan is contraindicated. The method used at baseline must be used consistently for postbaseline tumor assessments. Tumor assessment to be performed every 6 weeks (±7 days) from first treatment of Part B for the first year, and every 9 weeks (±7 days) thereafter even if treatment is delayed, until there is radiographic documentation of PD. Further radiographic assessments after treatment discontinuation will not be required for patients who discontinue for reasons other than radiographically documented PD.

l   Follow-up for the collection of survival data and subsequent anticancer treatments should be attempted after discontinuation of study treatment at regularly scheduled intervals (every 12 weeks ± 14 days) until sufficient OS-related information is collected. This follow-up might be a phone-call to the patient, her/his family, or local doctor.

Attachment 2. Protocol JVCW Study Schedule for the Continued Access Period

As described in Section 8.1.5, following study completion and sufficient overall survival (OS)-related information being collected, if there are patients receiving study treatment and experiencing ongoing clinical benefit, the study will enter the continued access period.

During the continued access period, 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. Lilly will collect only the data shown in the table below during the continued access period.

	Patients on Study Treatment During the Continued Access Period	**Continued Access Follow-Up[a]**
Visit	**501-50X**	**901**
Toxicity Assessments/AEs[b]	X	X
Immunogenicity[c]		
Ramucirumab PK Sample[c]		
Treatment Administration	X	

Abbreviations: AE = adverse event; PK = pharmacokinetics; SAE = serious adverse event.

a   No follow-up procedures will be performed for patients who withdraw participation. 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 ($\pm$7) days.

b   All AEs and SAEs will be reported as they were during previous periods of the trial.

c   In the event of an infusion-related reaction, blood samples will be collected for PK and immunogenicity analyses as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

Attachment 3. Protocol JVCW Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Research Sampling Schedule

Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Research Sampling Schedule

Sampling Time Point (Ramucirumab Infusion)	Pharmacokinetic Sample	Immunogenicity Sample	Whole Blood Sample for DNA	Plasma Sample	Archived Tumor Tissue Collection[a]
First-line (Part A)					
Day -14 to Cycle 1 (Visit 001) Day 1 Predose[b]	X[c]	X[c]	X[c,d]	X[c]	X[c]
Cycle 1 (Visit 001) Day 8 Predose[b]	X				
Cycle 2 (Visit 002) Day 1 Predose[b]	X	X			
Cycle 3 (Visit 003) Day 1 Predose[b]	X			X	
Cycle 5 (Visit 005) Day 1 Predose[b]	X	X			
Cycle 9 (Visit 009) Day 1 Predose[b]	X	X			
Every 4 cycles (Visit 013, 017-0XX) Day 1 Predose	X	X			
Pre-treatment period of Part B[e] (Visit 200)	X	X			
Second-line (Part B)					
Cycle 1 Day 1 (Visit 201) Predose[b]	X	X			
Cycle 2 Day 1 (Visit 202) Predose[b]	X	X			
Short-term safety follow-up (30 ±7d) (Visit 801)	X	X		X	

Abbreviations: C_{min} = minimum concentration; d = day; DNA = deoxyribonucleic acid; PK = pharmacokinetics.

a   Submission of tumor specimen is optional for participation in this study. Pathology notes for tumor samples may be requested.

b   Sampling should be done to evaluate trough level of ramucirumab, even if the sampling point is skipped due to ramucirumab treatment withhold or discontinuation. If a patient meets criteria for permanent discontinuation of ramucirumab/placebo (section 9.A.4.1.2), the subsequent collection of pharmacokinetic and immunogenicity samples in Part A should be discussed with the sponsor. In that case, the collection of pharmacokinetic and immunogenicity samples at Cycle 1 Day 1 (Visit 201) predose and Cycle 2 Day 1 (Visit 202) predose in Part B is not required.

c   Prior to the first infusion (baseline; may be obtained within 14 days prior to the initial infusion of ramucirumab/placebo on Day 1 of Cycle 1).

d   Prior to initial infusion of ramucirumab/placebo on Cycle 1 Day 1 is preferred; otherwise, later during the trial is acceptable.

e   If the patient does not move to Part B within 30 days after discontinuation from Part A, PK and immunogenicity samples will be collected. In this case, the preferable sampling timing is 30 ±7d after discontinuation from Part A.

Note: Pre-dose (C_{min}) sampling windows will allow 1 day before the dosing day (the same day as dosing is preferable).

Note: Heparin lock is not allowed. Saline lock is allowed. If heparin is used, blood samples will be collected from the line flushed with saline.

Pharmacokinetic and Immunogenicity Sampling Schedule for Infusion-related Reactions

In the event of an investigational infusion-related reaction, blood samples will be collected for both pharmacokinetic and immunogenicity analysis as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

Sampling Time Point	Pharmacokinetic Sample	Immunogenicity Sample
Onset of infusion-related reaction	X	X
Resolution of infusion-related reaction	X	X
30 days following infusion-related reaction	X	X

Note: In the case that an infusion-related reaction occurs during or just after ramucirumab infusion, blood samples will be collected from contralateral arm.

Note: Heparin lock is not allowed. Saline lock is allowed. If heparin is used, blood samples will be collected from the line flushed with saline.

Attachment 4. Protocol JVCW Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry[a]**:
Hemoglobin	**Serum Concentrations of**:
Hematocrit	Sodium
Erythrocyte count (RBC)	Magnesium
Mean cell volume (MCV)	Potassium
Mean cell hemoglobin concentration (MCHC)	Total bilirubin
Leukocytes (WBC)	Direct bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Platelets	Uric acid
	Calcium

Urinalysis[a]:

Routine dipstick measurements. If the dipstick test shows 2+ proteinuria, administer full dose of ramucirumab/placebo without interruption and perform a 24-hour collection or urine P/C ratio (urine protein/ creatinine ratio) prior to next cycle of ramucirumab/placebo.

Glucose (random)
Albumin

Clinical Chemistry:

Lactate dehydrogenase (to be collected at baseline)[a]
HgbA1c (to be collected at baseline and short-term follow-up)[b]

Thyroid Tests[b]:

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

Pregnancy Test (Serum or Urine, females only)[a]

Coagulation Tests[a]:

INR
activated Partial thromboplastin time (aPTT)

Ramucirumab concentrations[b]
Anti-ramucirumab antibody[b]

Abbreviations: HgbA1c = hemoglobin A1c; INR = international normalized ratio; RBC = red blood cells; TSH = thyroid-stimulating hormone; T4 = thyroxine; WBC = white blood cells.

[a] Assayed by investigator-designated (local) laboratory.
[b] Assayed by Lilly-designated (central) laboratory.

Attachment 5. Protocol JVCW Hepatic Monitoring Tests for Treatment-Emergent Abnormality

In the event that a patient experiences elevated alanine aminotransferase (ALT) >5x upper limit of normal (ULN) and elevated total bilirubin >2x ULN, clinical and laboratory monitoring should be initiated by the investigator as early as possible. 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 that are not specified below may also be required under specific circumstances to investigate the hepatic abnormality.

Hepatic Monitoring Tests

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma glutamyltransferase; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = International Normalized Ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

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

Attachment 6. Protocol JVCW 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:

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

For serum creatinine concentration in μmol/L:

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

[a] Age in years, weight (wt) in kilograms.
Reference: Cockcroft and Gault 1976.

Reference:

Cockcroft DW, Gault MD. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

Attachment 7. Protocol JVCW RECIST Criteria 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 (v.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, positron emission tomography (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.

<u>Cystic lesions</u>:

- 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.

<u>Lesions with Prior Local Treatment</u>:

- 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 Non-Target 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 case report form (eCRF) in millimeters (or decimal fractions of centimeters).

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 eCRF (eg, 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 (I.V.) contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT scan or MRI (with or without I.V. 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 only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (eg, 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 scan 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 and 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). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology and Histology: These techniques can be used to differentiate between partial responses (PR) and CR in rare cases if required by protocol (eg, 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 (eg, 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 scan is not recommended for lesion assessment. If a new lesion is found by PET scan, another assessment must be done by CT scan, unless the PET CT scanis of diagnostic quality. If a CT scan 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 CR or 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 non-target) 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 (eg, 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 (<10 mm 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 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. **Time Point Response: Patients with Target (± Nontarget) Disease**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not 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 = non-evaluable; PR = partial response; SD = stable disease; PD = progressive disease.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 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 = non-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 21 days 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. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target 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.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trials* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from randomization.

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).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Reference:

Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

Attachment 8. Protocol JVCW NCI-CTCAE v. 4.03 Infusion-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, I.V. fluids); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, I.V. fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

Abbreviations: I.V. = intravenously; NSAID = non-steroidal anti-inflammatory drug; po = orally.

Attachment 9. Protocol JVCW Concomitant Medications

Antiangiogenic class of medicines are known to be associated with increased risk of specific toxicities (eg, excessive bleeding). Specific toxicities are also associated with fluoropyrimidines and platinum agents. Adequate precautions on the use of concomitant medications need to be taken to minimize the occurrence of known adverse events. Below is a table highlighting select therapeutic interventions that require restricted use or that are not permissible for use while the patient is on study. *Note: analgesic medications other than non-steroidal anti-inflammatory drugs (NSAIDs) may be used as needed and for chronic use.*

Drug Class	May Use As Needed	May Use for Chronic Use	Conditions for Use
RAMUCIRUMAB RESTRICTIONS			
NSAIDs			Aspirin up to 325mg/day permitted. The chronic use of NSAIDs with a high risk of bleeding (eg, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged unless at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the patient. Chronic use of analgesic agents with no or low bleeding risk (eg, paracetamol/acetaminophen, metamizole, dipyrone, propyphenazone) is acceptable.
Warfarin	N	N	Use of warfarin is prohibited. See Inclusion Criterion [5].
GENERAL RESTRICTIONS/ALLOWANCES			
Colony-Stimulating Factors	Y	N	In accordance with ASCO guidelines.
Erythroid Growth Factors	Y	N	In accordance with ASCO guidelines.
Anticoagulants (except for warfarin)	Y	Y	Careful evaluation is required if patients need to be administered anticoagulation either prior to or during study treatment. Note that increased risk of hemorrhage is a boxed warning in the CYRAMZA package insert.
Additional concurrent chemotherapy	N	N	
Radiotherapy	N	N	Palliative radiotherapy during the study can be considered after consultation with the Lilly CRP or CRS.
Biologic response modifiers	N	N	
Other investigational agents	N	N	

Abbreviations: ASCO = American Society of Clinical Oncology; CRP = clinical research physician; CRS = clinical research scientist; INR = international normalized ratio; N = No; NSAID = non-steroidal anti-inflammatory drug; Y = Yes.

Attachment 10.   Protocol JVCW Urine Protein Algorithm

```
┌─────────────────────────────────────────────────────────────────────┐
│                  Urine dipstick prior to next R/P dose                 │
└─────────────────────────────────────────────────────────────────────┘

        ┌────────┐              ┌────────┐              ┌────────┐
        │  ≤1+   │              │   2+   │              │  ≥3+   │
        └────────┘              └────────┘              └────────┘
             │                       │                       │
             ▼                       ▼                       ▼
      ┌────────────┐          ┌────────────┐          ┌────────────┐
      │ Administer │          │ Administer │          │  Skip R/P  │
      │   R/P*     │          │   R/P*     │          │administration│
      └────────────┘          └────────────┘          └────────────┘
                                     │                       │
                                     ▼                       ▼
            ┌─────────────────────────────────────────────────────┐
            │       24-hour urine collection or P/C ratio           │
            │          3 days prior to next R/P dose                │
            └─────────────────────────────────────────────────────┘

        ┌────────┐              ┌────────┐              ┌────────┐
        │  <2 g  │              │  2-3 g │              │  >3 g  │
        └────────┘              └────────┘              └────────┘
             │                       │                       │
             ▼                       ▼                       ▼
      ┌────────────┐          ┌────────────┐          ┌────────────┐
      │ Administer │          │  Skip R/P  │          │ Discontinue│
      │   R/P*     │          │administration│        └────────────┘
      └────────────┘          │until recovery│
                              │  to <2 g*    │
                              └────────────┘
```
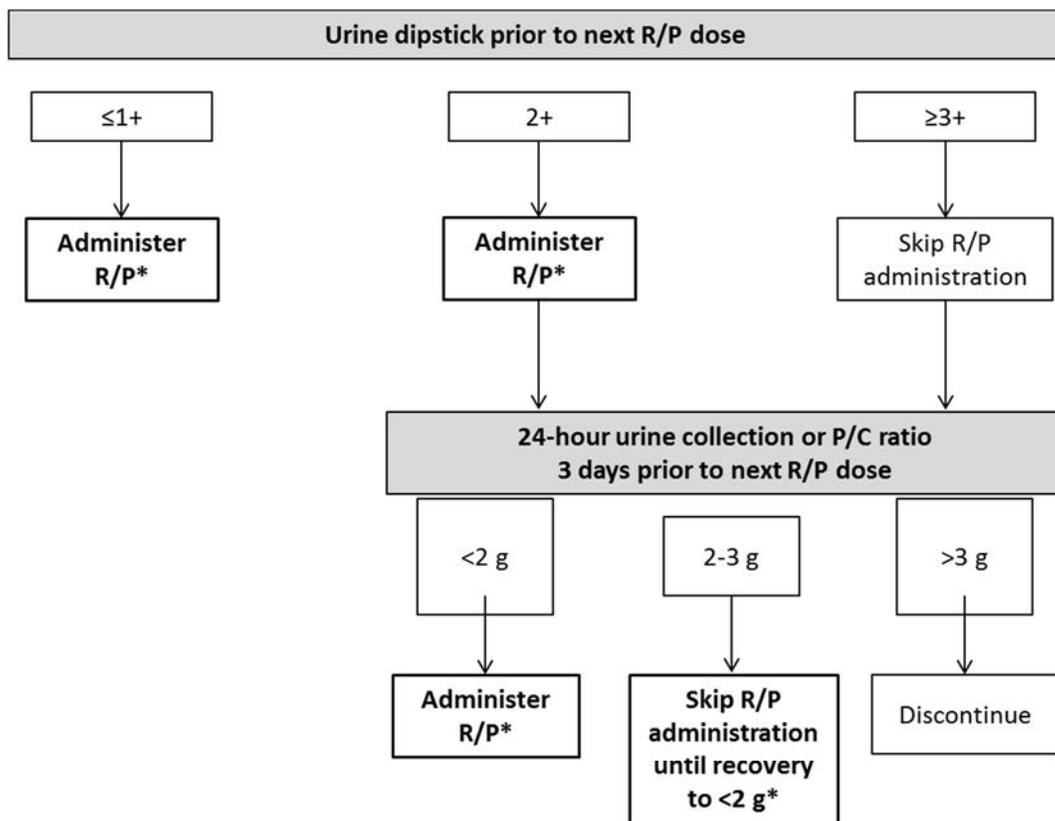
✱: Dose of R/P

# of proteinuria of ≥2 g	Dose of R/P
None	Full previous dose
First instance	Reduce 1 dose level[a]
Second instance	Reduce 1 dose level[a]

Abbreviations: P/C ratio = urine protein/creatinine ratio; R/P = ramucirumab/placebo.

[a] Dose level of R/P should be reduced 1 level down from prior dose level (8 -> 6 -> 5 mg/kg). If proteinuria persists after 5 mg/kg dose, then R/P should be discontinued.

Attachment 11. Protocol JVCW Amendment (c) Summary A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

---

Overview

Protocol I4T-JE-JVCW "A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of S-1 and Oxaliplatin With or Without Ramucirumab as First-line Therapy Followed by Paclitaxel With Ramucirumab as Second-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma" has been amended. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Section 9.B.4.1.1 and 9.B.4.1.6.: Added texts in Table JVCW.9.B.9. and Table JVCW.9.B.11.to align with Table JVCW.9.B.10.

- Attachment 3: Added texts to reduce the burden of the patient who permanently discontinued ramucirumab/placebo in the Part A.

Additional minor clarifications/correction, including but not limited to:

- Section 9.A.4: Added texts to clarify the ramucirumab/placebo administration.

- Attachment 1: Added texts to clarify the allowance of Cycle 1 Day 8 for Hematology, Serum chemistry, Urinalysis in Part A.

- Attachment 1: Corrected the footnote for Weight in Part A and Part B.

- Attachment 3: The footnote c can be applied to the samples of pharmacokinetic and immunogenicity on Day -14 to Cycle 1 (Visit 001) Day 1 Predose.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~.
	Additions have been identified by the use of <u>underscore</u>.

9.A.4. Selection and Timing of Doses

A cycle is defined as an interval of 21 days in Part A. (Note: A delay due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 days and not be counted as a protocol deviation. Additionally, in a circumstance where Lilly confirms that a delay will be permitted over 3 days, such as a New Year's holiday or similar, this instance will not be counted as a protocol deviation.)<u>.</u> A cycle will begin at the Day 1 administration of any component of chemotherapy treatment. <u>Ramucirumab/placebo cannot be administered on a consecutive third week even though the planned Day 1 of a new cycle is delayed due to delay of chemotherapy treatment.</u> In the event of discontinuation of S-1 and oxaliplatin, a new cycle will be started on Day 22 (Day 1 of the new cycle) with the administration of ramucirumab monotherapy. If a patient discontinues any component of study treatment, Day 1 will be based on the administration of the remaining study component(s).

9.B.4.1.1. Transition from Part A to Part B

Table JVCW.9.B.9.   Initiation Criteria of Part B

Criteria for Ramucirumab treatment	Ramucirumab related toxicities/AEs:	Grade <2 or baseline (except for hypertension, venous thromboembolic events, and proteinuria)
	Urine protein:	Dipstick <2+ <u>In case of dipstick ≥2+, perform a 24-hour urine collection or urine protein/creatinine ratio, and the 24-hour collection or urine protein/creatinine ratio need to show</u> ~~or~~ protein level <2 g/24 h<u>.</u>

9.B.4.1.6. Criteria for Starting Next Cycle (Part B)

Table JVCW.9.B.11.   Criteria for Ramucirumab Treatment – Part B

Urine protein:	Dipstick ~~<~~<u>≤</u>2+ <u>In case of dipstick 2+, perform a 24-hour urine collection or urine protein/creatinine ratio within 3 days prior to next ramucirumab dose administration, and the 24-hour collection or urine protein/creatinine ratio need to show</u>~~or~~ protein level <2 g/24 h<u>.</u>

Attachment 1.   **Protocol JVCW Study Schedule**

Study Schedule, Protocol I4T-JE-JVCW – Part A

g Height measurement to be performed during the Screening period of Part A only. Weight to be measured within 3 days prior to treatment at each ~~visit~~cycle. If there is a ≥10% change (increase or decrease) in body weight from the last dose calculation, then dose must be recalculated.

i Baseline laboratory assessments can be used for dosing for Cycle 1 Day 1. For subsequent visits, laboratory assessments must be performed within 3 days prior to <u>treatment on Cycle 1 Day 8, and</u> Day 1 and Day 8 of every <u>subsequent</u> cycle.

k Baseline lab assessments can be used for dosing for Cycle 1 Day 1. For subsequent cycles, lab assessments must be performed within 3 days prior to treatment on <u>Cycle 1 Day 8, and</u> Day 1 and Day 8 of every <u>subsequent</u> cycle.

l Routine dipstick measurements at baseline can be used for dosing for Cycle 1 Day 1. For subsequent cycles, routine dipstick measurements must be performed within 3 days prior to treatment on <u>Cycle 1 Day 8, and</u> Day 1 and Day 8 of every <u>subsequent</u> cycle. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection or urine protein/creatinine ratio must be obtained to assess protein. Test of urinalysis can be skipped if ramucirumab/placebo is not administered due to treatment delay/omission.

Study Schedule, Protocol I4T-JE-JVCW – Part B

c Weight to be measured within 3 days prior to treatment at each ~~visit~~cycle. If there is a ≥10% change (increase or decrease) in body weight from the last dose calculation, then dose must be recalculated.

Attachment 3. Protocol JVCW Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Research Sampling Schedule

Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Translational Research Sampling Schedule

Sampling Time Point (Ramucirumab Infusion)	Pharmacokinetic Sample	Immunogenicity Sample	Whole Blood Sample for DNA	Plasma Sample	Archived Tumor Tissue Collection[a]
First-line (Part A)					
Day -14 to Cycle 1 (Visit 001) Day 1 Predose[b]	X[c]	X[c]	X[c,d]	X[c]	X[c]

b Sampling should be done to evaluate trough level of ramucirumab, even if the sampling point is skipped due to ramucirumab treatment withhold or discontinuation. <u>If a patient meets criteria for permanent discontinuation of ramucirumab/placebo (section 9.A.4.1.2), the subsequent collection of pharmacokinetic and immunogenicity samples in Part A should be discussed with the sponsor. In that case, the collection of pharmacokinetic and immunogenicity samples at Cycle 1 Day 1 (Visit 201) predose and Cycle 2 Day 1 (Visit 202) predose in Part B is not required.</u>

Leo Document ID = 3410e839-499e-40d3-ae2d-acd90d3af972

Approver: PPD
Approval Date & Time: 29-Aug-2016 00:28:54 GMT
Signature meaning: Approved

Approver: PPD)
Approval Date & Time: 29-Aug-2016 10:04:13 GMT
Signature meaning: Approved