Protocol I4T-CR-JVCR (c)

A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab (IMC-1121B) in Patients with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma, Refractory to or Progressive after First-Line Therapy with Platinum and Fluoropyrimidine

NCT02898077

Approval Date: 14-Mar-2019

1. Protocol I4T-CR-JVCR(c) A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab (IMC-1121B) in Patients with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma, Refractory to or Progressive after First-Line Therapy with Platinum and Fluoropyrimidine

Ramucirumab (IMC-1121B, LY3009806)

This is a randomized, placebo-controlled, double-blind, multicenter, Phase 3 study of patients with advanced gastric or gastroesophageal junction adenocarcinoma, refractory to or progressive after first-line therapy with platinum and fluoropyrimidine. Patients will be randomized to receive either paclitaxel plus ramucirumab or paclitaxel plus placebo. Treatment will continue until disease progression, unacceptable toxicity, or meeting other treatment discontinuation criteria.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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2. Synopsis

Study Rationale

In China, gastric cancer is the second most common cancer and is the third leading cause of cancer death. In the first-line setting in advanced gastric cancer, platinum/fluoropyrimidine regimens form the backbone of chemotherapy. Meanwhile, in the second-line setting, there has been no standard regimen established for gastric cancer to date. The high incidence and mortality of gastric cancer and relatively limited chemotherapeutic options after first-line therapy underpin the need for research in second-line therapeutic options.

One promising approach to the treatment of cancer is inhibition of angiogenesis by targeting the vascular endothelial growth factor (VEGF) pathway. Ramucirumab (IMC-1121B, LY3009806) is a recombinant human monoclonal antibody that specifically binds to the extracellular domain of VEGF Receptor 2 (VEGFR-2) with high affinity as demonstrated in animal models. A Phase 3 global study (I4T-IE-JVBD [JVBD]) demonstrated that ramucirumab monotherapy plus best supportive care (BSC) following disease progression on initial therapy could improve overall survival (OS; median 5.2 months versus 3.8 months, hazard ratio [HR] = 0.776, 95% confidence interval [CI] = 0.603 to 0.998, p=.0473) and progression-free survival (PFS; median 2.1 months versus 1.3 months, HR = 0.483, 95% CI = 0.376 to 0.620, p<.0001) as compared with placebo plus BSC in patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Furthermore, preclinical and clinical data have shown that the addition of agents targeting the VEGF pathway can improve the efficacy of chemotherapy, providing a rationale to investigate the efficacy and safety of adding ramucirumab to a commonly used second-line chemotherapeutic drug such as paclitaxel in advanced gastric cancer. Accordingly, another Phase 3 global study (I4T-IE-JVBE [JVBE]) was designed to demonstrate the superiority of ramucirumab plus paclitaxel comparing with placebo plus paclitaxel in patients with advanced gastric or GEJ adenocarcinoma after failure of first-line therapy with platinum and fluoropyrimidine. Study JVBE demonstrated that ramucirumab plus paclitaxel as a combination therapy for patients improves OS (median 9.6 months versus 7.4 months, HR = 0.807, 95% CI = 0.678 to 0.962, p=.0169) and PFS (median 4.4 months versus 2.9 months, HR = 0.635, 95% CI = 0.536 to 0.752, p<.0001) as compared with paclitaxel monotherapy. Based on the results of these 2 Phase 3 studies, ramucirumab was approved by the United States Food and Drug Administration as a single agent, as well as in combination with paclitaxel, for the treatment of advanced or metastatic gastric or GEJ adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

To further confirm the results of Study JVBE in a predominantly East Asian population, this multicenter randomized study is designed to evaluate the efficacy and safety of paclitaxel plus ramucirumab versus paclitaxel plus placebo in patients with advanced gastric or GEJ adenocarcinoma, refractory to or progressive after first-line therapy with platinum and fluoropyrimidine.

Clinical Protocol Synopsis: Study I4T-CR-JVCR

Name of Investigational Product: Ramucirumab (IMC-1121B, LY3009806)	
Title of Study: A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab (IMC-1121B) in Patients with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma, Refractory to or Progressive after First-Line Therapy with Platinum and Fluoropyrimidine	
Number of Planned Patients: Entered: 500 Randomized: 450	**Phase of Development:** 3
Length of Study: Planned first patient visit: November 2016 Planned last patient visit: July 2020 Planned interim analysis: An interim analysis is planned with a total of 256 PFS events.	
Objectives: The co-primary objective of this study is to evaluate PFS and OS in patients treated with paclitaxel plus ramucirumab (IMC 1121B) versus paclitaxel plus placebo as second-line treatment in patients with advanced gastric or GEJ adenocarcinoma after failure of any platinum and fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin). The secondary objectives of the study are to evaluate: • Time to progression • Objective response rate • Duration of objective response • Safety profile • Patient-reported outcome measures In addition, exploratory objectives include: • To explore biomarkers relevant to gastric or GEJ adenocarcinoma or safety, efficacy, and mechanism of action of ramucirumab.	
Study Design: This is a multicenter, randomized study evaluating the efficacy and safety of paclitaxel plus ramucirumab using a double-blind, placebo-controlled design. Approximately 450 patients will be randomized on a 2:1 ratio to receive either Arm A (paclitaxel plus ramucirumab) or Arm B (paclitaxel plus placebo) to observe at least 336 deaths. Randomization will be stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) (0 versus 1) and peritoneal metastases (yes versus no). Patients will continue to receive all treatments until there is radiographic or symptomatic progression of disease, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. Patients will undergo radiographic assessment of disease status according to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, every 6 weeks (±5 days), following the first dose of study therapy for the first 6 months and every 9 weeks (±5 days) thereafter, until documentation of radiographic progressive disease (PD). During postdiscontinuation follow-up, all patients will be followed for survival at regularly scheduled intervals (every 8 weeks [+0 to 7 days]) for as long as the patient is alive, or until the study completion.	
Diagnosis and Main Criteria for Inclusion and Exclusion: Male and female patients (age ≥18 years) with histologically or cytologically confirmed advanced gastric or GEJ adenocarcinoma who have received at least 1 cycle of therapy with any platinum and fluoropyrimidine as first-line treatment of their gastric adenocarcinoma, and who have experienced documented disease progression during first-line therapy, or within 4 months after the last dose of first-line therapy prior to study entry, will be randomized and treated at the investigational centers.	
Test Product, Dosage, and Mode of Administration: Ramucirumab drug product (DP), injection for intravenous (IV) use, 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 IV infusion at a dose of 8 mg/kg on Days 1 and 15 of a 4-week cycle. The infusion should be delivered over approximately 60 minutes. The infusion rate should not exceed 25 mg/minute.	

Reference Therapy, Dose, and Mode of Administration:

Ramucirumab DP placebo injection for IV use, 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 (at a volume equivalent to a dose of 8 mg/kg) on Days 1 and 15 of a 4-week cycle.

Paclitaxel, administered over approximately 60 minutes according to manufacturer standards, at a dose of 80 mg/m^2 on Days 1, 8, and 15 of a 4-week cycle.

Note: Premedication is required prior to infusion of paclitaxel according to the manufacturer's instructions and local standards. Premedication may consist of dexamethasone 20 mg orally administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine 300 mg or ranitidine 50 mg IV 30 to 60 minutes before paclitaxel. An antiemetic (such as ondansetron 8 mg IV or equivalent) administered 30 to 120 minutes before paclitaxel is recommended.

Planned Duration of Treatment:

Study treatment period: A treatment cycle will be defined as 28 days (4 weeks) in each arm and include the period of treatment with paclitaxel given on Days 1, 8, and 15, in combination with either ramucirumab or ramucirumab placebo given on Days 1 and 15. The period during which no treatment will be administered is required for patients to recover from toxicities to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 Grade <2 or baseline (with the exception of alopecia), and is expected to last for 14 days. Patients will continue to receive all treatments until there is radiographic or symptomatic progression of disease, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent.

Short-term follow-up period (postdiscontinuation): Approximately 30 days (no more than 37 days).

Long-term follow-up period (postdiscontinuation): After the decision is made to discontinue study treatment, follow-up information regarding further anticancer treatment and survival status will be collected at least every 8 weeks (+0 to 7 days). For patients who discontinue treatment for any reason other than radiographically documented PD (for example, symptomatic deterioration), information on disease progression (radiographic assessment) will also be collected until PD is documented by imaging. Follow-up will continue as long as the patient is alive, or until study completion, whichever is first.

Criteria for Evaluation:

Efficacy:

Progression-free survival is defined as the time from the date of randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1, or death due to any cause, whichever is first.

Overall survival is defined as the time from the date of randomization to the date of death from any cause.

Time to progression is defined as the time from the date of randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1.

Objective response rate is defined as the proportion of randomized patients achieving a best overall response of partial response (PR) or complete response (CR).

Duration of objective response is measured from the time measurement criteria first met for CR or PR (whichever is first recorded) to the date of the first radiographically documented PD as defined by RECIST, Version 1.1, or death due to any cause, whichever is first.

Assessment for response, according to RECIST, Version 1.1, will be performed every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD.

Safety:

Safety will be evaluated based on reported adverse events (AEs), clinical laboratory assessments, vital signs, and physical examinations. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Clinical laboratory toxicity and AEs will be graded using the NCI-CTCAE, Version 4.03.

Health Outcomes:

The assessment of quality of life and health status will be conducted using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30), and EuroQol-5 Dimension-3 Level (EQ-5D-3L), respectively.

Translational Research:

Whole blood samples may be used for DNA/genotype analysis and may include an examination of genes associated with angiogenesis, the mechanism of ramucirumab, and/or cancer, including but not limited to, VEGFR-2 and VEGF-A. Plasma samples may be analyzed for potential pharmacodynamic markers, including, but not necessarily limited to, placental growth factor, VEGF-A, VEGF-C, VEGF-D, soluble VEGFR-1, and soluble VEGFR-2. In addition, collection of tumor tissue samples will be strongly recommended for potential evaluation of tumor-specific mutations, VEGFR-2 expression, VEGFR-2 copy number variability, and other cancer-associated biomarkers.

Statistical Methods:

Statistical:

Approximately 450 patients will be randomized to the 2 treatment arms in a 2:1 ratio (300 patients in Arm A [paclitaxel plus ramucirumab] and 150 patients in Arm B [paclitaxel plus placebo]) in order to obtain at least 336 deaths. Assuming an exponential distribution in each arm and a true underlying HR of 0.81 as observed in the global study, 336 deaths will provide at least 80% probability to assure that the effect size observed in this study is consistent with the global study. Also assuming a constant accrual rate of 12 patients/month, a median OS of 10.5 months in Arm B and a median OS of 13 months in Arm A, the study will take approximately 44 months to obtain the required 336 deaths (37 months for accrual and 7 months for the follow-up). The primary PFS analysis and an interim OS analysis will be performed when at least 256 PFS events have occurred.

Efficacy:

The analysis of PFS/OS in this study is to estimate the HR and its 2-sided 95% CIs in a stratified Cox's proportional hazards model using treatment arm as a single covariate. The stratification factors included in the Cox model are ECOG PS (0 versus 1) and peritoneal metastases (yes versus no). A sensitivity analysis with an unstratified Cox proportional hazards model will be employed. Stratified (using the same stratification factor) and unstratified log-rank tests will also be conducted. The survival curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% CIs for median PFS/OS will be computed by the Brookmeyer and Crowley method. Landmark survival rates will also be estimated using KM estimates on the survival curve for each randomized arm. Associated 2-sided 95% CIs will also be calculated.

Safety:

Safety analyses will be performed on all randomized patients who receive at least 1 dose of study treatment. Safety analyses will include summaries of the incidence of AEs by maximum CTCAE grade (Version 4.03) that occur during the study treatment period or within 30 days after the decision is made to discontinue study treatment.

Health Outcomes:

QLQ-C30 and EQ-5D-3L analyses will be performed on all randomized patients with 1 baseline assessment and ≥1 postbaseline assessment. They will be analyzed descriptively by treatment arm.

Translational Research:

Translational research will be performed to analyze relevant biomarkers and their correlation to clinical outcomes.

3. Table of Contents

A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab (IMC-1121B) in Patients with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma, Refractory to or Progressive after First-Line Therapy with Platinum and Fluoropyrimidine

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4. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
AST	aspartate aminotransferase
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
bFGF	basic fibroblast growth factor
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 final database lock. 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.
BOR	best overall response
BP	blood pressure
BSC	best supportive care
CHF	congestive heart failure
CI	confidence interval
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product

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.
CR	complete response
CrCl	creatinine clearance
CRF/eCRF	case report form/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.
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC101	mouse antibody counterpart of ramucirumab
DCR	disease control rate
DOR	duration of objective response
DP	drug product
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EORTC	European Organization for Research and Treatment of Cancer
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient (includes short-term follow-up).
EQ-5D-3L	EuroQol-5 Dimension-3 Level Questionnaire
ERB/IRB	ethical review board/institutional 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.

extension period	The period between study completion and end of trial during which patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until one of the criteria for discontinuation is met.
FDA	Food and Drug Administration
GCP	good clinical practice
GEJ	gastroesophageal junction
GI	gastrointestinal
GPS	Global Patient Safety
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IMC-1121B	ramucirumab, LY3009806
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
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
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
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

IV	intravenous
IWRS	interactive web response system
KM	Kaplan-Meier product-limit method
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.
mAb	monoclonal antibody
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition scan
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PlGF	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
PRO	patient-reported outcome
PS	performance status
PVC	polyvinyl chloride
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	quality of life
randomize	The process of assigning patients to an experimental group on a random basis.
RECIST	Response Evaluation Criteria in Solid Tumors

rescreen	To screen 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
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, x-rays, CT/MRI, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	Patient who does not meet one or more criteria required for participation in a trial.
SD	stable disease
SDF1a	stromal cell-derived factor 1a
study completion	This study will be considered complete after the final analyses of overall survival are performed.
SUSARs	suspected unexpected serious adverse reactions
TTP	time to progression
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WOCBP	women of child-bearing potential

A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab (IMC-1121B) in Patients with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma, Refractory to or Progressive after First-Line Therapy with Platinum and Fluoropyrimidine

5. Introduction

Gastric cancer is a common malignancy with significant mortality rates; two-thirds of patients present with advanced disease at diagnosis (Pozzo and Barone 2008). In China, gastric cancer is the second most common cancer and the third leading cause of cancer death (Chen et al. 2015). The National Central Cancer Registry reported that there were 420,489 new cases and 297,496 deaths in 2011 (Chen et al. 2015). Because of its significant mortality rates and poor prognosis, new treatments are urgently required.

In the past decade, cytotoxic chemotherapy remains the cornerstone of treatment for gastric cancer. In the first-line setting in advanced gastric cancer, platinum/fluoropyrimidine regimens form the backbone of chemotherapy. Triplet regimens, such as adding an anthracycline or taxane, result in better outcomes. However, triplet regimens are reserved only for selected patients due to toxicity. Meanwhile, in the second-line setting, there has been no standard regimen established for gastric cancer to date. Several Phase 3 trials have demonstrated that monotherapies in second-line, such as paclitaxel, docetaxel, and irinotecan, are superior to best supportive care (BSC), resulting in longer survival (Thuss-Patience et al. 2011; Kang et al. 2012; Hironaka et al. 2013; Ford et al. 2014). Weekly administration of paclitaxel (at a dose of 80 mg/m^2) has become a common practice for second-line treatment in gastric cancer. However, only marginal improvements in patient outcomes have been achieved.

The progress of targeted therapy in gastric cancer has been slow as compared with other common cancers, such as breast, colorectal, and lung cancers. With the results of ToGA trial, trastuzumab in combination with chemotherapy has demonstrated a survival benefit as first-line therapy in human epidermal growth factor 2 positive gastric cancer patients (Bang et al. 2010). Many other molecular targeted agents are still undergoing clinical trials.

Vascular endothelial growth factor (VEGF) is expressed in gastric cancer, and it has been associated with more aggressive clinical disease (Feng et al. 2002). Previous studies showed that VEGF inhibition was effective in inhibiting gastric cancer growth (Jung et al. 2002). The AVAGAST trial, designed to evaluate the efficacy and safety of adding bevacizumab to fluoropyrimidine-cisplatin in the first-line treatment of advanced gastric cancer, was the first Phase 3 evaluation of an antiangiogenic agent with chemotherapy in advanced gastric cancer. However, this trial did not reach its primary objective; the median overall survival (OS) was 12.1 months with bevacizumab plus fluoropyrimidine-cisplatin and 10.1 months with placebo plus fluoropyrimidine-cisplatin (hazard ratio [HR] = 0.87; 95% confidence interval [CI] = 0.73 to

1.03; p=.1002) (Ohtsu et al. 2011). Regional analysis indicated that patients enrolled in North America and Latin America appeared to have a survival benefit with the addition of bevacizumab, whereas patients enrolled in Asia (90% from Japan and Korea) appeared to have no benefit. In Chinese patients with advanced gastric cancer, the results from the AVATAR trial also have demonstrated that bevacizumab plus capecitabine and cisplatin did not significantly improve outcomes (Shen et al. 2015). These results necessitate further investigation of agents targeting the VEGF pathway in gastric cancer by refining the selection of the patient population.

Ramucirumab (IMC-1121B, LY3009806) is a recombinant human immunoglobulin G, subclass 1 (IgG1) receptor-targeted monoclonal antibody (mAb) that specifically binds to the extracellular domain of vascular endothelial growth factor receptor 2 (VEGFR-2) with high affinity. Preclinical studies showed that the mouse antibody counterpart of ramucirumab (DC101) therapy is associated with significant reductions in tumor vascularity (as measured by cluster of differentiation 31 expression) and increase in endothelial and tumor apoptosis, resulting in reduced tumor growth in gastric cancer xenografts (Jung et al. 2002). DC101 has conferred enhanced antitumor effect when combined with cytotoxic agents, such as paclitaxel in murine models of human prostate and bladder cancers (Inoue et al. 2000; Sweeney et al. 2002).

A Phase 1 clinical study (I4T-IE-JVBM [JVBM]) has demonstrated that ramucirumab monotherapy, administered at doses ranging from 2 to 16 mg/kg every week in patients with advanced cancer, achieved an objective response rate (ORR) of 10.8% and a disease control rate (DCR) of 64.9% (Spratlin et al. 2010). In particular, 1 patient with gastric cancer had confirmed partial response (PR) lasting 103 weeks. In a Phase 3 global study (I4T-IE-JVBD [JVBD]) in patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma, ramucirumab as a single agent plus BSC versus placebo plus BSC, reduced the risk of death by 22% (HR = 0.776; 95% CI = 0.603 to 0.998; p=.0473), resulting in a 37% longer median survival in the ramucirumab arm (5.2 months versus 3.8 months, a difference of 1.4 months). Progression-free survival (PFS) was largely improved as well (median 2.1 months versus 1.3 months, HR = 0.483; 95% CI = 0.376 to 0.620; p<.0001). Additionally, ramucirumab was well tolerated in this patient population, as demonstrated by similar rates between the ramucirumab and placebo arms for most adverse events (AEs). The most frequent AEs of Grade ≥3 were: hypertension (7.6% ramucirumab, 2.6% placebo); fatigue (6.4% ramucirumab, 10.0% placebo); anemia (6.4% ramucirumab, 7.8% placebo); abdominal pain (5.9% ramucirumab, 2.6% placebo); decreased appetite (3.4% ramucirumab, 3.5% placebo); and bleeding/haemorrhage (3.4% ramucirumab, 2.6% placebo) (Fuchs et al. 2014).

Furthermore, the possibility of combining ramucirumab with an active chemotherapeutic drug was also explored. Preclinical and clinical data have shown that the addition of agents targeting the VEGF pathway can improve the efficacy of taxane regimens (Enzinger et al. 2006; Shah et al. 2011). A Phase 1b study (I4T-IE-JVBW [JVBW]) investigating weekly paclitaxel with ramucirumab in 6 Japanese patients with advanced gastric adenocarcinomas demonstrated that the combination was safe and well-tolerated. There were no dose-limiting toxicities in this study. The DCR and the ORR were 100% and 16.7%, respectively (Ueda et al. 2015). The Phase 3 global study (I4T-IE-JVBE [JVBE]) was designed to demonstrate efficacy in patients treated with paclitaxel plus ramucirumab compared to patients treated with paclitaxel plus

placebo as second-line treatment in metastatic gastric or GEJ adenocarcinoma after failure of any platinum and fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin). Study JVBE demonstrated that ramucirumab plus paclitaxel as a combination therapy for patients with advanced gastric cancer improves OS (median 9.6 months versus 7.4 months, HR = 0.807; 95% CI = 0.678 to 0.962; p=.0169) and PFS (median 4.4 months versus 2.9 months, HR = 0.635; 95% CI = 0.536 to 0.752; p<.0001) as compared with paclitaxel monotherapy (Wilke et al. 2014). Based on these results, ramucirumab was approved by the United States Food and Drug Administration (FDA) as a single agent, as well as in combination with paclitaxel, for treatment of advanced or metastatic gastric or GEJ adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. Besides second-line treatment, there is another ongoing Phase 3 study (I4T-MC-JVCU [JVCU]) investigating efficacy and safety of capecitabine (or 5-fluorouracil) and cisplatin with or without ramucirumab in the first-line setting of metastatic gastric or GEJ adenocarcinoma.

To investigate the same combination regimen in a predominantly East Asian population, this confirmatory study is specifically designed to evaluate the efficacy and safety of ramucirumab in combination with paclitaxel in patients with advanced gastric or GEJ adenocarcinoma that have failed standard therapy with platinum and fluoropyrimidines.

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 the investigational product 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.

6. Objectives

6.1. Primary Objective

The co-primary objective of this study is to evaluate PFS and OS in patients treated with paclitaxel plus ramucirumab (IMC-1121B, LY3009806) versus paclitaxel plus placebo as second-line treatment in patients with advanced gastric or GEJ adenocarcinoma after failure of any platinum and fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin).

6.2. Secondary Objectives

Secondary objectives are to evaluate:

- Time to progression (TTP)
- ORR
- Duration of objective response (DOR)
    - Safety profile
    - Patient-reported outcome (PRO) measures

6.3. Exploratory Objectives

The exploratory objectives of the study include:

- To explore biomarkers relevant to gastric or GEJ adenocarcinoma or safety, efficacy, and mechanism of action of ramucirumab.

7. Study Population

Male and female patients (age ≥18 years) with histologically or cytologically confirmed advanced gastric or GEJ adenocarcinoma who have received at least 1 cycle of therapy with any platinum and fluoropyrimidine as first-line treatment of their gastric adenocarcinoma, and who have experienced documented disease progression during first-line therapy, or within 4 months after the last dose of first-line therapy prior to study entry, will be randomized and treated at the investigational centers. A record of the most recent cancer- and noncancer-related screening/baseline evaluations will be reviewed to determine the eligibility of a patient for this study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. If a patient is considered for rescreening, the investigator must contact the Lilly Medical Monitor or designee. Individuals may be rescreened up to 2 times. The interval between rescreenings should be at least 1 week. Each time rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Study participants should be instructed not to donate blood or blood products during the study or for 12 weeks following the last dose of study drugs.

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

[2] Are at least 18 years of age (or of an acceptable age according to local regulations, whichever is older) at the time of randomization.

[3] Have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at study entry (see Attachment 6).

[4] Have a histopathologically or cytologically confirmed diagnosis of gastric or GEJ adenocarcinoma.

[5] Have metastatic disease or locally advanced, unresectable disease.

[6] Have at least 1 measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (see Attachment 7). Positron emission tomography (PET) scans and ultrasounds may not be used for diagnostic purposes.

[7] Have experienced documented objective radiographic or symptomatic disease progression (for example, any new or worsening malignant effusion documented by ultrasound examination) which may be confirmed by pathologic criteria (histology and/or cytology) if appropriate, during first-line therapy, or within 4 months after the last dose of first-line therapy with any platinum/fluoropyrimidine doublet (acceptable prior platinum agents are cisplatin, carboplatin, or oxaliplatin; acceptable prior fluoropyrimidine agents are 5-fluorouracil, capecitabine, or S-1) with or without anthracycline (epirubicin or doxorubicin) for unresectable or metastatic disease.

[8] Have resolution to Grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, of all clinically significant toxic effects of chemotherapy, surgery, radiotherapy, or hormonal therapy (with the exception of alopecia), except where otherwise noted in this eligibility criteria.

[9] Have adequate organ function, defined as:

- Total bilirubin ≤1.5 times (×) the upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3× ULN for AST/ALT if no liver metastases, ≤5× ULN if liver metastases.
- Serum creatinine ≤1.5× ULN or calculated creatinine clearance (CrCl; per the Cockcroft-Gault [1976] formula or equivalent and/or 24-hour urine collection) ≥50 mL/min (Cockcroft and Gault 1976; see Attachment 8).
- Absolute neutrophil count (ANC) ≥1.5× 10^9/L, 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 ≥100× 10^9/L.
- International Normalized Ratio (INR) ≤1.5 or prothrombin time ≤1.5× ULN.
- Partial thromboplastin time/activated partial thromboplastin time (PTT/aPTT) ≤1.5× ULN.

[10] Have urinary protein ≤1+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine sample must be collected and must demonstrate <1000 mg of protein in 24 hours to allow participation in the study.

[11] If female, are surgically sterile, postmenopausal, or compliant with a highly effective contraceptive method (failure rate <1%) during and for 12 weeks after the treatment period (oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method). If male, are surgically sterile or compliant with a highly effective contraceptive regimen during and for 6 months after the treatment period. The label (for example, Summary of Product Characteristics, United States Package Insert, and so on) requirements with regard to the methods and duration of contraception during and after treatment with paclitaxel can differ between countries. Country specific requirements will apply only if they are more stringent than those already stipulated in the protocol.

[12] Have an estimated life expectancy of at least 12 weeks, in the judgment of the investigator.

7.2. Exclusion Criteria

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

[13] Have squamous cell or undifferentiated gastric cancer.

[14] Have undergone major surgery within 28 days prior to randomization, or have had a central venous access device placement within 7 days prior to randomization, except if the procedure is minimally invasive (for example, introduction of peripherally inserted central catheter [PICC] line) and the investigator does not anticipate any significant bleeding.

[15] Have received any first-line chemotherapy other than platinum and fluoropyrimidine with or without anthracycline for advanced gastric or GEJ adenocarcinoma.

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

[17] Have received any previous systemic therapy (including investigational agents) targeting VEGF or the VEGFR signaling pathways. Other previous targeted therapies (for example, trastuzumab) are permitted, if stopped at least 28 days prior to randomization.

[18] Have a history of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to randomization.

[19] Are receiving therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents. Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that the coagulation parameters defined in the inclusion criteria (INR ≤1.5) are met.

[20] Are receiving ongoing therapy with nonsteroidal anti-inflammatory agents (NSAIDs; for example, indomethacin, ibuprofen, naproxen, or similar agents) or other antiplatelet agents (for example, clopidogrel, ticlopidine, dipyridamole, and anagrelide). Aspirin (acetylsalicylic acid) at doses of ≤325 mg/day is permitted.

[21] Have significant bleeding disorders, vasculitis, or had a significant bleeding episode from the gastrointestinal (GI) tract within 3 months prior to study entry.

[22] Have a history of GI perforation and/or fistulae within 6 months prior to randomization.

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

[24] Have experienced any arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to randomization.

[25] Have uncontrolled arterial hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg) despite standard medical management.

[26] Have a serious or nonhealing wound, peptic ulcer, or bone fracture within 28 days prior to randomization.

[27] Have a bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea.

[28] Have a serious illness or medical condition(s) including, but not limited to the following:

- Known human immunodeficiency virus infection or acquired immunodeficiency syndrome-related illness
- Active or uncontrolled clinically serious infection
- Previous or concurrent malignancy, except for basal or squamous cell skin cancer and/or in situ carcinoma of the cervix, or other solid tumors treated curatively and without evidence of recurrence for at least 3 years prior to the study
- Uncontrolled metabolic disorders or other nonmalignant organ or systemic diseases or secondary effects of cancer that induce a high medical risk and/or make assessment of survival uncertain

- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient ineligible for entry into this study
- History or evidence of known central nervous system metastases or carcinomatous meningitis
- Child-Pugh B cirrhosis (or worse)
- Cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis
- Known allergy or hypersensitivity to mAb treatment or any components used in the ramucirumab drug product (DP) preparation
- Known allergy or hypersensitivity to paclitaxel or any components used in the paclitaxel preparation or other contraindication for taxane therapy.

[29] Are pregnant or breastfeeding.

[30] Are currently enrolled in, or have been discontinued within the last 28 days from, a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the investigational drug/device used in this study), or 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.

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 [13] and [15] specify the patient population that is intended for enrollment. Exclusion criteria [14], [18] - [27] are for patient safety based on what is known about the side effect profile of an antiangiogenic agent such as ramucirumab. Exclusion criteria [17], [28], and [30] are to prevent previously administered systemic therapy targeting VEGF or the VEGFR signaling pathways, investigational therapy, or comorbidity, from confounding an assessment of safety/efficacy in this study. Exclusion criterion [28] is also to prevent enrollment of patients whose prognosis may be particularly poor. Exclusion criteria [16] and [29] are also written in the interest of patient safety.

7.3. Discontinuations

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 Patients

7.3.1.1. Discontinuation from All Study-Related Therapy

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 clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the Lilly CRP does not agree with the investigator's determination it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

In addition, the investigator should withdraw a patient from all study-related therapy for any of the following reasons:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator decision
    - The investigator decides that the patient should be discontinued from the study or study drugs.
    - If 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 drugs occurs prior to introduction of the new agent.
- Patient decision
    - The patient or the patient's designee (for example, parents or legal guardian) requests to be withdrawn from the study or study drug. (If the patient withdraws consent to treatment, he or she may still enter long-term follow-up if follow-up consent is not withdrawn.)
- Sponsor decision
    - 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).
- Radiographic progression as defined in Attachment 7 or symptomatic progression of disease.
- An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient), which in the opinion of the investigator cannot be attributed to a specific study agent.

- A Grade 3 to 4 infusion-related reaction (IRR) which in the opinion of the investigator cannot be attributed to a single study agent (considered at least possibly related to each study agent).
- Any therapy-related event that is deemed life-threatening, regardless of grade.
- Any event which would require study therapy to be modified by more than 2 dose reductions, or to be held for more than 28 days from the last administered dose, and is considered at least possibly related to both study agents (paclitaxel and ramucirumab/placebo).
- An intercurrent illness or change in the patient's condition that renders the patient unsuitable for further treatment, in the opinion of the investigator.
- Protocol noncompliance with this study protocol. Patients who miss appointments shall be contacted by site personnel to determine the reason for the missed appointment and to try to reschedule the appointment. The date(s) the patient was contacted and the type of contact used should be recorded in the study documentation.

The reason and date for discontinuation will be collected for all patients. All randomized patients who discontinue, regardless of whether they received study drug or not, will have procedures performed as shown in the Study Schedule (Attachment 1).

7.3.1.2. Discontinuation from Ramucirumab/Placebo Therapy

The investigator may withdraw a patient from ramucirumab/placebo therapy for any of the following reasons:

- An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient) that is, in the opinion of the investigator, attributed to ramucirumab/placebo (and considered unrelated or unlikely related to paclitaxel).
- A Grade 3 to 4 IRR that is attributed to ramucirumab (and unrelated or unlikely related to paclitaxel).
- A Grade 3 to 4 arterial thromboembolic event.
- Any Grade 3 to 4 venous thromboembolic event that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy.
- Any venous thromboembolic event occurring or intensifying during anticoagulant therapy.
- A Grade 3 to 4 bleeding or hemorrhagic event.
- Grade 4 hypertension or persistent/recurrent hypertension as detailed in Section 9.4.2.1.2.
- Proteinuria >3 g/24-hours or persistent/recurrent proteinuria >2 g/24-hours, as detailed in Section 9.4.2.1.5.
- Any Grade 4 (life-threatening) nonhematologic toxicity considered by the investigator to be possibly, probably, or definitely related to ramucirumab/placebo.
- Gastrointestinal perforation.
- Any Grade 3 to 4 events consistent with CHF.
- Any event which would warrant ramucirumab/placebo therapy to be modified by more than 2 dose reductions or to be held for >28 days from the last administered dose, and is

clearly attributed to ramucirumab/placebo (that is, recurrent or persistent hypertension or proteinuria).
- New occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

7.3.1.3. Discontinuation from Paclitaxel Therapy

The investigator may withdraw a patient from paclitaxel therapy for any of the following reasons:

- An unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient) and is, in the opinion of the investigator, clearly attributed to paclitaxel (and considered unrelated or unlikely related to ramucirumab/placebo)
- A Grade 3 to 4 infusion reaction that is attributed to paclitaxel (and considered unrelated or unlikely related to ramucirumab/placebo).
- Any event which would warrant paclitaxel therapy to be modified by more than 2 dose reductions or to be held for >28 days from the last administered dose, and is clearly attributed to paclitaxel (that is, recurrent or persistent neuropathy).

The Lilly Medical Monitor will be consulted before a patient is discontinued from the study due to paclitaxel intolerance.

7.3.1.4. Continuation of Therapy On-Study in the Setting of Discontinuation of One Component of Therapy

If 1 therapeutic agent is permanently discontinued secondary to toxicity, then therapy with the other study agents should continue and the patient should remain on-study with full adherence to all protocol related requirements. Patients who have paclitaxel discontinued may continue to receive ramucirumab/placebo on-study, provided they continue to meet entry criteria and do not have evidence of disease progression. Patients who have ramucirumab/placebo discontinued (that is, in the setting of Grade 4 hypertension or proteinuria) may receive ongoing paclitaxel therapy on-study, provided they continue to meet entry criteria and do not have evidence of disease progression.

After termination of study therapy, the patient will be treated as clinically indicated by the investigator or referring physician. All patients will be followed until resolution or stabilization of any SAE or study-related toxicity. If the reason for withdrawal from the trial is the death of the patient, the 2 options for categorizing withdrawal are either progressive disease (PD) or an AE (>1 AE may be documented as a reason for withdrawal). Only 1 event will be recognized as the cause of death. If a patient is discontinued from all study therapy:

- The reasons for discontinuation should be documented in the patient's medical record and electronic case report form (eCRF).
- For patients who discontinue for reasons other than radiographic PD, radiographic assessment for tumor response should continue every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD.

- A follow-up evaluation begins the day after the decision is made to discontinue study treatment and lasts approximately 30 days (no more than 37 days) as described in Section 8.1.2.1. The patient should be followed for survival at regularly scheduled intervals (at least every 8 weeks [+0 to 7 days]) for as long as he or she remains alive (until study completion as defined in Section 8.1.3); for additional details, please see Section 8.1.2.2.

7.3.2. Discontinuation of Study Sites

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

7.3.3. Discontinuation of the Study

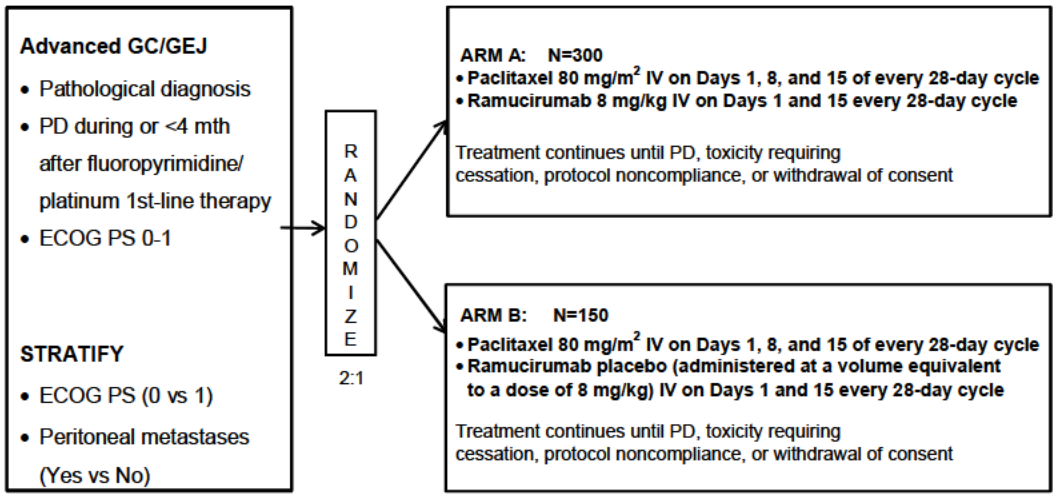
The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

Study I4T-CR-JVCR (JVCR) is a multinational, randomized, multicenter, double-blind, placebo-controlled, Phase 3 study in patients with histologically or cytologically confirmed advanced gastric or GEJ adenocarcinoma, refractory to or progressive after first-line therapy with platinum and fluoropyrimidine. Approximately 450 patients will be randomized on a 2:1 ratio to Arm A (paclitaxel plus ramucirumab) and Arm B (paclitaxel plus placebo) to observe at least 336 deaths. Randomization will be stratified by ECOG PS (0 versus 1) and peritoneal metastases (yes versus no).

Figure JVCR 8.1 illustrates the study design.



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gastric cancer; GEJ = gastroesophageal junction adenocarcinoma; IV = intravenous; mth = months; N = number of patients; PD = progressive disease.

Figure JVCR 8.1. Illustration of study design for Study I4T-CR-JVCR.

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

- **Baseline:** begins when the ICF is signed and ends at the first study treatment (or discontinuation, if no treatment is given)
- **Study Period:** begins at the first study treatment and ends at study completion. The study period does not include the extension period.
    - **Study 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.
    - **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.

Short-term follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (no more than 37 days).

Long-term follow-up begins 1 day after short-term follow-up is completed and continues until the patient's death or overall study completion to collect additional data (for example, survival data).

- **Extension Period:** begins after study completion and ends at the end of trial. During the extension period, patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until one of the criteria for discontinuation is met. Crossover may be permitted to the control arm. The extension period includes extension period follow-up.
    - **Extension Period Follow-Up:** begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the extension period and lasts approximately 30 days (no more than 37 days).

Baseline radiographic assessment of disease will be performed within 21 days prior to randomization; first treatment will be administered within 7 days following randomization.

Patients in both arms will receive any necessary premedication (see Section 9.1.1) prior to the first infusion of study therapy at each treatment session. Following necessary premedication, patients will receive the following treatments:

- Experimental Arm A:
    - Ramucirumab DP 8 mg/kg intravenous (IV) on Days 1 and 15 of every 28-day cycle
    - Paclitaxel 80 mg/m^2 IV on Days 1, 8, and 15 of every 28-day cycle
- Placebo Arm B:
    - Ramucirumab DP placebo (administered at a volume equivalent to a dose of 8 mg/kg) IV on Days 1 and 15 of every 28-day cycle
    - Paclitaxel 80 mg/m^2 IV on Days 1, 8, and 15 of every 28-day cycle

Administration of all therapeutic products will occur as described in Section 9.1.

A treatment cycle will be defined as 28 days (4 weeks) in each arm and includes the period of treatment with paclitaxel given on Days 1, 8, and 15, in combination with either ramucirumab or ramucirumab placebo given on Days 1 and 15. The period during which no treatment will be administered is required for patients to recover from toxicities to NCI-CTCAE, Version 4.03 criteria Grade <2 or baseline (with the exception of alopecia), and is expected to last 14 days.

Patients will undergo radiographic assessment of disease status every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD. Patients in both arms will continue to receive all treatments until there is radiographic or symptomatic progression of disease, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent. In case of treatment discontinuation for any reason other than radiographically confirmed PD, radiographic tumor

assessments will continue every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD.

Follow-up information regarding further anticancer treatment and survival status will be collected at least every 8 weeks (+0 to 7 days). Long-term follow-up will continue as long as the patient is alive, or until study completion (as defined in Section 8.1.3), whichever is first.

Clinical assessments for safety will occur as described in Section 8.1 and Section 10.3. Adverse event information will be collected approximately 30 days (no more than 37 days) after the decision is made to discontinue study treatment and until all SAEs and all therapy-related AEs have resolved, stabilized, returned to baseline, or been deemed irreversible.

Patients with evidence of sustained clinical benefit (that is, no disease progression) may continue to receive study drug(s) for long-term durations during the extension period.

Upon study completion (see Section 8.1.3), investigators and patients may be unblinded to study treatment assignment.

The Lilly CRP will notify investigators in the event of study closure.

8.1.1. Baseline and Study Period Assessments

8.1.1.1. Screening/Baseline

Screening/baseline evaluations used to determine the patient's study eligibility must be completed within 28 days prior to randomization unless otherwise specified. Written informed consent must be obtained prior to any study-specific evaluations and prior to receiving treatment. All patients must undergo the following evaluations:

- Demography (year of birth, sex, race/ethnicity)
- Medical history (any preexisting toxicity within 28 days prior to randomization should be documented and recorded as part of the medical history)
- Assessment of baseline toxicity/AEs and conditions (to be conducted within 14 days prior to randomization)
- Physical examination (including height and weight measurements and calculation of body surface area; to be conducted within 14 days prior to randomization)
- Vital signs (including temperature, pulse rate, respiratory rate, and blood pressure; within 14 days prior to randomization)
- ECOG PS evaluation (within 21 days prior to randomization)
- Concomitant medication assessment, including all medications taken within 28 days prior to randomization (to be conducted within 14 days prior to randomization)
- Hematology profile (within 7 days prior to randomization; packed red blood cell transfusions are not allowed within 1 week prior to baseline hematology profile)
- Coagulation profile (within 7 days prior to randomization)
- Full serum chemistry profile (within 7 days prior to randomization)
- Urinalysis (within 14 days prior to randomization)

- Serum β-human chorionic gonadotropin pregnancy test for women of child-bearing potential (WOCBP) (within 7 days prior to randomization)
- Imaging studies (computed tomography [CT]/magnetic resonance imaging [MRI]) and tumor assessment as described in Section 10.1 (within 21 days prior to randomization)
- Electrocardiogram (ECG; within 21 days prior to randomization)
- Echocardiogram/multi-gated acquisition scan (MUGA; within 21 days prior to randomization)
- Patient-reported outcomes assessment (within 14 days prior to randomization) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EuroQol-5 Dimension-3 Level (EQ-5D-3L) questionnaire, to be completed at the beginning of the visit, before blood sampling or any extensive contact and consultation with the clinician/study investigator; such encounters may thereafter bias patient responses. The instruments should be administered together and in sequence order, with the EORTC QLQ-C30 presented first, followed by presentation of the EQ-5D-3L.
- Sampling for translational research as describe in Section 10.4.2.

Results of all screening/baseline evaluations must be reviewed by the principal investigator or his or her physician designee to ensure that all eligibility criteria have been satisfied prior to enrollment. If a patient is not to be randomized, the reason for ineligibility must be recorded.

8.1.1.2. Treatment Period

A series of clinical tests and procedures will be performed throughout the study as described below and in the Study Schedule (Attachment 1).

Evaluations/procedures to be performed prior to and at the completion of each infusion include:

- Vital sign measurements, including temperature, pulse rate, respiration rate, and blood pressure, before and at the completion of each infusion of ramucirumab or placebo and before and at the completion of each infusion of paclitaxel. If paclitaxel is administrated within 30 minutes after the completion of ramuciumab/placebo infusion, the measurement of vital signs before paclitaxel administration is optional.

Evaluations/procedures to be performed on Days 1, 8, and 15 of each cycle include:

- Toxicity/AE assessment
- Concomitant medication assessment
- Hematology profile (within 36 hours prior to treatment [blood may be collected the morning of study therapy or the day before, results to be available and evaluated prior to start of infusion] on Days 1, 8, and 15 of each cycle until discontinuation of paclitaxel; thereafter, prior to the start [Day 1] of every 28-day cycle only. Baseline lab assessments can be used for dosing for Cycle 1 Day 1 if performed within 7 days prior to Cycle 1 Day 1.)
- Serum ALT, AST, and total bilirubin (within 36 hours prior to treatment [blood may be collected the morning of study therapy or the day before, results to be available and evaluated prior to start of infusion] on Days 1, 8, and 15 of each cycle until

discontinuation of paclitaxel; thereafter, to be collected along with full serum chemistry profile prior to the start [Day 1] of every 28-day cycle only, Baseline lab assessments can be used for dosing for Cycle 1 Day 1 if performed within 7 days prior to Cycle 1 Day 1.)
- Urinalysis (Days 1 and 15 only)
- Sampling for plasma pharmacodynamic biomarker (before the fourth and seventh infusions of ramucirumab/placebo).

Evaluations/procedures to be performed prior to the start (Day 1) of each cycle only include:

- Physical examination (to include weight; height does not need to be repeated beyond the initial evaluation)
- ECOG PS evaluation
- Full serum chemistry profile (within 36 hours prior to treatment).

Evaluations to be performed for WOCBP, Electrocardiogram, Echocardiogram/MUGA and Coagulation profile are scheduled as below:

- Serum or urine pregnancy test for WOCBP (within 3 days prior to Day 1 of every odd-numbered cycles or in accordance with local regulations, whichever is of shorter duration)
- Electrocardiogram (within 3 days prior to the first infusion of Cycles 2, Cycle 3, and then every odd-numbered cycles, thereafter, within 30 days after the discontinuation of ramucirumab/placebo and within 30 days after the discontinuation of paclitaxel)
- Echocardiogram/MUGA (within 3 days prior to the first infusion of Cycle 3 only, within 30 days after the discontinuation of ramucirumab/placebo, and within 30 days after the discontinuation of paclitaxel)
- Coagulation profile (within 3 days prior to Day 1 of every odd-numbered cycles and can be performed more frequently if clinically indicated)

Evaluations to be performed every 6 weeks (±5 days) following the first dose of study therapy include:

- Imaging studies/tumor assessments, including CT/MRI of all known disease, as described in Section 10.1 and Attachment 7, will be performed every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until radiographic documentation of PD, even if therapy is delayed due to toxicity or for other reasons.

Evaluations to be performed prior to each cycle following the first dose of study therapy include:

- Patient reported outcomes. This does not need to be completed prior to Cycle 1 if screening/baseline assessment was completed.

8.1.2. Postdiscontinuation Follow-Up

All patients should be followed and AEs reported for approximately 30 days during short-term follow-up. Other follow-up assessments will be conducted as shown in the Study Schedule (Attachment 1).

8.1.2.1. Short-Term Follow-Up

End-of-therapy occurs after the decision is made to discontinue study therapy. In all cases, the primary reason for discontinuation will be captured in the eCRF.

All AEs occurring after the patient receives the first dose of study treatment until 30 days after the decision is made to discontinue study treatment must be reported to the Sponsor or its designee via eCRF. The short-term follow-up begins the day after the decision is made to discontinue study treatment and lasts approximately 30 days (no more than 37 days):

- Physical examination with weight measurement
- Vital signs
- ECOG PS evaluation
- Toxicity/AE assessment
- Serum or urine pregnancy test for WOCBP
- Hematology
- Full serum chemistry profile
- Coagulation profile
- Electrocardiogram
- Echocardiogram/MUGA
- Urinalysis
- Concomitant medication assessment
- Patient-reported outcomes (PROs)

All SAEs and AEs considered at least possibly-related to study therapy will be followed until resolved, stabilized, returned to baseline, or deemed irreversible.

For patients who discontinue treatment for reasons other than radiographic PD, imaging studies with tumor measurements/disease response assessments will continue to be performed every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD.

If it is deemed to be in the best interest of the patient to start a new anti-cancer treatment prior to the scheduled end of the short-term follow-up visit, the follow-up visit duration may be shortened. In this case, the short-term follow-up assessments should be completed prior to the initiation of the new therapy.

8.1.2.2. Long-Term Follow-Up

Patients will be contacted at least every 8 weeks (+0 to 7 days) to obtain information about survival status and detailed information on any subsequent systemic anticancer therapy and disease progression (for patients not having a radiographic progression). Long-term follow-up will continue as long as the patient is alive, or until study completion (as defined in Section 8.1.3).

8.1.3. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the interim analysis (256 PFS events) if the study is stopped early, or following the final analysis of OS (336 deaths; see Section 12) if the study is not stopped early, as determined by Lilly.

Investigators will continue to follow the Study Schedule for all patients until notified otherwise by Lilly.

"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 the 30-day short-term safety follow-up in the extension period. If no patients enter the extension period, study completion will occur at the same time as the end of trial (that is, the date of the last visit of the last scheduled procedure shown in the Study Schedule for the last patient) in this study.

The study can be stopped at any time by the institutional review board/acting ethics committee or the Sponsor because of safety considerations or futility.

Figure JVCR 8.2 provides an illustration of study completion, the extension period, and the end of trial.

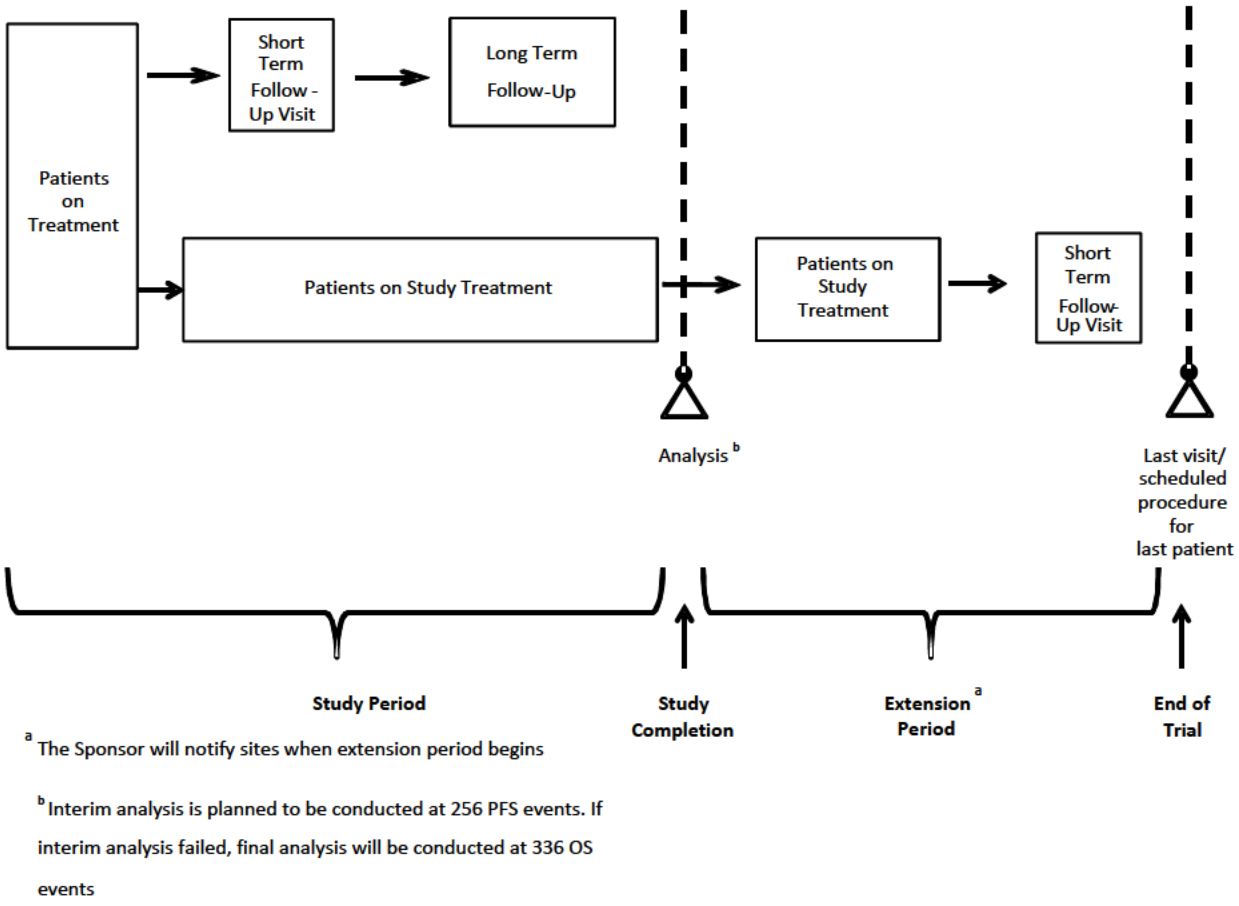


Figure JVCR 8.2. Study completion, the extension period, and the end of trial.

8.1.4. Extension Period

After study completion, all patients who are on study treatment and who are eligible for the extension period will be unblinded. Patients receiving study treatment and experiencing ongoing clinical benefit and no undue risks may continue to receive study treatment in the extension period until one of the criteria for discontinuation is met (Section 7.3). During the extension period, placebo will no longer be administered. If the study shows early efficacy at interim (as defined in Section 12.2.12), or shows efficacy at final analysis, subjects randomized to the control arm may be permitted to crossover to the treatment arm under investigator discretion. Lilly will notify investigators when the extension period begins.

Patients who are in short-term follow-up when the extension period begins will continue in short-term follow-up until the short-term follow-up visit is completed. Long-term follow-up does not apply. Patients who are in long-term follow-up when the extension period begins will be discontinued from long-term follow-up.

During the extension period, the following information will be collected according to Attachment 2:

- All AEs will be reported on the case report form (CRF). Serious adverse events will also be reported on the CRF and to Lilly Global Patient Safety (GPS; see Section 10.3.1). 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.
- Drug administration information
- Reason for study therapy discontinuation

During the extension period, routine safety and efficacy monitoring, including radiographic evaluation of disease and laboratory testing, such as pregnancy testing, should be continued as necessary, and documentation retained within the source files, to confirm patient eligibility to continue on treatment or the 30-day short-term follow-up visit. 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.

8.2. Discussion of Design and Control

This study will be conducted since the prognosis for patients with advanced gastric cancer is generally poor, and there is a great unmet medical need for novel treatments. Paclitaxel has been extensively studied as second-line chemotherapy in advanced gastric cancer patients, using a schedule consisting of 80 mg/m^2 administered once a week for 3 weeks followed by a 1-week rest period (Hironaka et al. 2006; Kodera et al. 2007). This treatment, with the addition of placebo, will act as the control arm of this study. The study arm will add ramucirumab (8 mg/kg IV on Days 1 and 15 of every 28-day cycle) to weekly paclitaxel, with the objective of evaluating the efficacy and safety of ramucirumab plus weekly paclitaxel as second-line therapy among patients with advanced gastric cancer. This ramucirumab dose is the same as that used in the global Phase 3 Study JVBE.

Investigational treatment administration in this study is double-blind; that is, patients, investigational sites, and the sponsor study team do not have immediate access to treatment assignments for any patients. Randomization in this study will be stratified by ECOG PS (0 versus 1) and peritoneal metastases (yes versus no). Both factors were independent prognostic factors for OS in global Studies JVBD and JVBE.

9. Treatment

9.1. Treatments Administered

Following necessary premedication, patients will receive the following treatments:

- Experimental Arm A:
  - Ramucirumab DP 8 mg/kg IV on Days 1 and 15 of every 28-day cycle
  - Paclitaxel 80 mg/m^2 IV on Days 1, 8, and 15 of every 28-day cycle.
- Placebo Arm B:
  - Ramucirumab DP placebo (administered at a volume equivalent to a dose of 8 mg/kg) IV on Days 1 and 15 of every 28-day cycle
  - Paclitaxel 80 mg/m^2 IV on Days 1, 8, and 15 of every 28-day cycle.

On Days 1 and 15 of each cycle, following premedication, ramucirumab/placebo will be administered over approximately 60 minutes. Administration will be followed by a 1-hour observation period, and subsequently by administration of paclitaxel over approximately 60 minutes. The 1-hour observation period between administration of ramucirumab/placebo and paclitaxel is mandatory for the first 2 cycles, but may be omitted in Cycle 3 and beyond, provided there has been no evidence of IRR.

Any measurements used to determine dose should be taken at each cycle, and dose should be recalculated for each cycle.

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

- Explaining the correct use of the drug(s) and planned duration of each individual's treatment to the site personnel
- Verifying that protocol instructions are followed properly
- Maintaining accurate records of study drug storage, dispensing, and collection
- Returning all unused medication, if not already destroyed by the site, to Lilly or its designee at the end of the study.

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

9.1.1. Premedication

Premedication is recommended prior to infusion of ramucirumab DP or placebo. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at investigator discretion. Premedication must be provided in the setting of a prior Grade 1 to 2 IRR, as detailed in Section 9.4.2.1.1.
All premedication administered must be adequately documented in patient's source charts and on the eCRF.

Premedication is required prior to infusion of paclitaxel according to the manufacturer's instructions and local standards. Premedication may consist of dexamethasone 20 mg orally administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its

equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine 300 mg or ranitidine 50 mg IV (or equivalent) 30 to 60 minutes before paclitaxel. An antiemetic (such as ondansetron 8 mg IV or equivalent) administered 30 to 120 minutes before paclitaxel is recommended.

When ramucirumab/placebo and paclitaxel are administered subsequently on the same day (that is, Days 1 and 15 of each cycle), it is sufficient to administer diphenhydramine hydrochloride and dexamethasone only once, prior to administration of ramucirumab/placebo.

9.1.2. Ramucirumab Drug Product or Placebo

Aseptic technique is to be used when preparing and handling ramucirumab or placebo. Patients will receive ramucirumab or placebo by IV infusion over approximately 60 minutes at 8 mg/kg on Days 1 and 15 of every 28 days in the absence of disease progression or other withdrawal criteria.

Patients will receive ramucirumab/placebo via IV infusion over approximately 60 minutes. The infusion rate should not exceed 25 mg/minute. In the event that the infusion time takes longer than 60 minutes (based on the patient's body weight), the infusion time should be accurately recorded on the eCRF. The first dose of ramucirumab (or placebo) is dependent upon the patient's screening/baseline body weight in kilograms. Subsequent doses of ramucirumab (or placebo) must be recalculated if there is a ≥10% change (increase or decrease) in body weight from the time of the most recent dose calculation; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in body weight from the time of the most recent dose calculation. 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 within 30 days prior to dose. If no recent dry weight is available, actual weight will be used.

Ramucirumab is compatible with common infusion containers. The use of a low protein binding 0.22 micron in–line filter is recommended. Based on the calculated volume of ramucirumab, add (or remove from pre-filled [with 0.9% normal saline] IV 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 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 (that is, 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.

CAUTION: Infusion-related reactions may occur during or following ramucirumab or placebo administration.

9.1.3. Paclitaxel

Investigators should consult the manufacturer's instructions for paclitaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of paclitaxel.

Aseptic technique is to be used when preparing and handling paclitaxel. Patients will receive paclitaxel by IV infusion over approximately 60 minutes at 80 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle.

The first dose of paclitaxel is dependent upon the patient's baseline body surface area. Subsequent doses of paclitaxel must be recalculated if there is a ≥10% change (increase or decrease) in body surface area from baseline; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in body surface area from baseline.

Paclitaxel must be diluted prior to infusion. When reconstituting paclitaxel, please follow the current local product labeling instructions. Paclitaxel should be diluted in 0.9% sodium chloride (normal saline) injection, United States Pharmacopeia (USP) or local equivalent; 5% dextrose injection, USP or local equivalent; 5% dextrose and 0.9% sodium chloride injection, USP or local equivalent; or 5% dextrose in Ringer's injection, to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery to the solution through IV tubing containing an in-line (0.22 micron) filter.

Data collected for the presence of the extractable plasticizer di-[2-ethyl-hexyl] phthalate show that levels increase with time and concentration when dilutions are prepared in polyvinyl chloride (PVC) containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

9.2. Materials and Supplies

9.2.1. Ramucirumab Drug Product

Ramucirumab DP is a sterile, preservative-free solution for infusion formulated in histidine buffer at a ramucirumab drug substance 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.

9.2.2. Ramucirumab Drug Product Placebo

Placebo is a sterile, preservative-free solution for infusion formulated in histidine buffer. The buffer contains 10mM histidine, 75mM sodium chloride, 133mM 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.

9.2.3. Paclitaxel

Investigators should consult the provided paclitaxel package insert for complete packaging and labeling information.

9.3. 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). The IWRS registration consists of assigning the patient a unique study identification number and randomizing the patient to 1 of the 2 treatment arms. Once the patient is registered through the IWRS, he/she is considered to be enrolled in the study.

Randomization will be stratified by ECOG PS (0 versus 1) and peritoneal metastases (yes versus no). To balance the treatment allocation among the stratification factors, a stratified permuted block randomization will be utilized and incorporated into the IWRS.

9.4. Selection and Timing of Doses

Patients will receive either paclitaxel plus ramucirumab or paclitaxel plus placebo (see Section 8.1). Study drug will be administered as shown in Section 9.1.

A treatment cycle is defined as 28 days (4 weeks). It is recognized that in the course of clinical cancer care, it is not always possible to schedule therapeutic infusions at precise intervals (because of holidays, travel difficulties, or other circumstances). Accordingly, infusions administered within 3 days before or after the planned infusion time point will be considered acceptable. Deviations beyond this window are strongly discouraged, and require Sponsor (or designee) approval.

9.4.1. Special Treatment Considerations

9.4.1.1. Treatment Requirements and Delays

9.4.1.1.1. Requirements Prior to Day 1 of Each Treatment Cycle

Prior to Day 1 of each administration of study therapy, hematology, urine protein (dipstick), liver, and renal function must be adequate as required in Table JVCR 9.1 and Table JVCR 9.2. Preinfusion laboratory data may not be older than 36 hours. For AE/toxicities not listed in Table JVCR 9.1 and Table JVCR 9.2, treatment delay is at investigator discretion.

Table JVCR 9.1. Criteria for Paclitaxel Treatment on Day 1 of Each Cycle

Parameter	Criterion
Neutrophils	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Hemoglobin	≥8 g/dL
Serum Creatinine	≤1.5× ULN or calculated creatinine clearance ≥50 ml/min
Bilirubin	≤1.5× ULN
AST/ALT	≤3× ULN if no liver metastases, ≤5× ULN if liver metastases

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; min = minute; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

Table JVCR 9.2. Criteria for Ramucirumab Treatment on Day 1 of Each Cycle

Parameter	Criterion
Urine Protein	Dipstick <2+ or protein level <2 g/24-hr
Specific Adverse Event of Ramucirumab	Refer to 9.4.2.1

Abbreviations: AE = adverse event; hr = hour; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

If 1 or more criteria outlined in the tables above are not met at the time of a planned treatment, the following general rules for the management of treatment delays apply:

- In the case of paclitaxel-related toxicity or abnormal laboratory values, blood counts and serum chemistry will be repeated weekly. The start of the next cycle will be delayed until recovery to the values stated above. However, ramucirumab/placebo therapy should continue as scheduled until the next cycle has resumed. When the subsequent cycle of paclitaxel is initiated, administration of ramucirumab/placebo and paclitaxel will be resynchronized according to the study design described in this protocol (that is, 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, provided the criteria outlined in Table JVCR 9.2 are met.
- In the case of ramucirumab/placebo-related toxicity, ramucirumab/placebo will be delayed for 1 week and administered on Day 8 (and Day 15) of the treatment cycle provided that ramucirumab/placebo-related toxicities have resolved to Grade <2 or baseline (except for hypertension, venous thromboembolic events, and proteinuria). If toxicities have not resolved on Day 8, ramucirumab/placebo will be delayed for another week and administered on Day 15 according to the schedule described in this protocol. In both cases, paclitaxel will continue according to the planned schedule.
- If a patient cannot be treated with 1 component of the study therapy (paclitaxel or ramucirumab) for more than 28 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.

- If the start of a cycle is delayed due to toxicity, radiographic assessment of disease response should not be delayed, but should be performed every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD.

9.4.1.1.2. Requirements Prior to Days 8 and 15 of Each Treatment Cycle

Prior to Days 8 and 15 of each administration of study therapy, hematology, urine protein (dipstick), and liver function must be adequate (see Table JVCR 9.3 and Table JVCR 9.4). Preinfusion laboratory data may not be older than 36 hours. For AE/toxicities not listed in Table JVCR 9.3 and Table JVCR 9.4, treatment delay is at investigator discretion.

Table JVCR 9.3. Criteria for Paclitaxel Treatment on Days 8 and 15 of Each Cycle

Parameter	Criterion
Absolute neutrophil count	$\geq 1.0 \times 10^9$/L
Platelet count	$\geq 75 \times 10^9$/L
Hemoglobin	≥8 g/dL
Bilirubin	≤1.5× ULN
AST/ALT	≤3× ULN if no liver metastases, ≤5× ULN if liver metastases

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

Table JVCR 9.4. Criteria for Ramucirumab Treatment on Day 15 of Each Cycle

Parameter	Criterion
Urine Protein	Dipstick <2+ or protein level <2 g/24-hr
Specific Adverse Event of Ramucirumab	Refer to 9.4.2.1

Abbreviations: AE = adverse event; hr = hour; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

If 1 or more criteria outlined in the tables above are not met at the time of a planned treatment, the following general rules for management of treatment delays apply:

- In the case of paclitaxel-related toxicity or abnormal laboratory values (Table JVCR 9.3) on Days 8 or 15, paclitaxel will be skipped that day. No dose reductions are allowed within a given cycle
- In the case of ramucirumab-related toxicity on Day 15 (Table JVCR 9.4), paclitaxel will be administered according to the planned schedule, but ramucirumab will be delayed for 1 week and administered on Day 22 of the treatment cycle, provided that ramucirumab-related toxicities have resolved to Grade <2 or baseline (except for hypertension, venous thromboembolic events, or proteinuria). 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 (except for hypertension, venous thromboembolic events, and proteinuria).

9.4.2. General Dose Modifications: Ramucirumab

Dose modifications are permitted for ramucirumab/placebo in the setting of non-life-threatening and reversible Grade 3 clinical AEs (for example, fever) considered to be at least possibly related to ramucirumab/placebo and that resolve to Grade ≤1 or pretreatment baseline within 1 treatment cycle (approximately 28 days). If a Grade 4 AE occurs and is deemed at least possibly related to ramucirumab/placebo, then ramucirumab/placebo should be discontinued except in the specific case of Grade 4 fever or Grade 4 laboratory abnormalities. If Grade 4 fever or laboratory abnormalities resolve to Grade ≤1 or pretreatment baseline within 1 treatment cycle (approximately 28 days), treatment with investigational product may be continued at the discretion of the investigator. In these settings, ramucirumab/placebo may be readministered. If a second instance of such an event occurs, ramucirumab/placebo should be subsequently readministered at a dose of 6 mg/kg every other week. A second dose reduction to 5 mg/kg every other week is permitted for this level of event (Grade 3 or 4 event). If the dose of ramucirumab/placebo is reduced because of potentially related AEs, subsequent dose increases are not permitted. Note that this section of the protocol pertains only to general dose modifications. Criteria for dose reduction in the setting of various specific AEs may be found in Section 9.4.2.1. Ramucirumab/placebo will be permanently discontinued in case of any ramucirumab/placebo-related event that is deemed life-threatening, regardless of grade.

Patients who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE, v 4.03, Grade 1 or 2 AEs should not have dose reductions related to the persistence or mild worsening of those symptoms or laboratory values; dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the investigator. Except in the case of proteinuria, as described in Section 9.4.2.1.5, asymptomatic laboratory abnormalities should not result in dose interruptions, modifications, or discontinuation of study therapy unless determined by the investigator to be clinically significant or life-threatening.

9.4.2.1. Treatment Guideline and Dose modification for Specific Adverse Events of Ramucirumab

Ramucirumab should be administered to patients only according to the inclusion and exclusion criteria specified in the clinical study protocol.

Ramucirumab must not be administered to patients with previous severe (Grade 3 or 4) hypersensitivity reactions to ramucirumab.

Ramucirumab should not be administered to patients who have a known allergy to any of the ingredients used in the DP formulation.

Adverse events of concern, which may or may not be associated with ramucirumab therapy, may include IRRs, hypertension, arterial or venous thromboembolic events, bleeding (hemorrhagic)

events, GI perforation, proteinuria, CHF, surgery and impaired wound healing, liver injury/liver failure, and reversible posterior leukoencephalopathy syndrome (RPLS).

9.4.2.1.1. Ramucirumab Infusion-Related Reactions

Any treatment-related IRRs are defined according to the NCI-CTCAE, Version 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 described above should be graded as shown in Table JVCR 9.5.

Table JVCR 9.5. NCI-CTCAE, Version 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 (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr	Prolonged (e.g., 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 an 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 (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hr	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., 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.					

NCI-CTCAE, Version 4.03, Infusion-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cytokine-release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr	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 (e.g., 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: e.g. = for example; hr = hour; IV = intravenous; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs = nonsteroidal anti-inflammatory drugs.

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

The following are treatment guidelines for IRRs:

Grade 1

- Slow the infusion rate by 50%
- Monitor the patient for worsening of condition
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion

Grade 2

- Stop the infusion
- Administer diphenhydramine hydrochloride 50 mg IV (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 IV (or equivalent); additional premedication may be administered at the investigator's discretion

For a second Grade 1 or 2 IRR, administer dexamethasone 8 to 20 mg IV (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8 to 20 mg IV (or equivalent). When ramucirumab/placebo and paclitaxel are administered subsequently on the same day (that is, Days 1 and 15 of each cycle), it is sufficient to administer diphenhydramine hydrochloride and dexamethasone only once, prior to administration of ramucirumab/placebo.

Grade 3

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride IV (or equivalent, per institutional guidelines), dexamethasone IV (or equivalent, per institutional guidelines), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.
- Patients who have a Grade 3 IRR will not receive further ramucirumab (or placebo) treatment, but will continue to be followed on the protocol.

Grade 4

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride IV (or equivalent, per institutional guidelines), dexamethasone IV (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 4 IRR will not receive further ramucirumab (or placebo) treatment, but will continue to be followed on the protocol.

If a patient should have an IRR to ramucirumab/placebo, 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. In addition, these same samples may be assessed for levels of ramucirumab and for pharmacodynamic markers to provide information on the nature of the IRR. The procedure for sample collection and handling is described in a separate procedural manual.

9.4.2.1.2. Hypertension

The following are treatment guidelines for hypertension (an expected AE in patients receiving ramucirumab) that develops during the study:

Grade <3

- If the hypertension is not associated with symptoms, continue ramucirumab (or placebo) therapy and initiate antihypertensive therapy.
- If the hypertension is associated with symptoms, hold ramucirumab (or placebo) therapy until symptoms resolve and initiate antihypertensive therapy.

- If ramucirumab (or placebo) therapy is held for hypertension (that is, symptomatic hypertension, markedly elevated blood pressure [BP] unresponsive to antihypertensive therapy), the dose of ramucirumab (or placebo) should be reduced upon retreatment to 6 mg/kg every 2 weeks. A second dose reduction to 5 mg/kg every 2 weeks should be undertaken if an additional postponement of therapy is required.

Grade 3 (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg; medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated)

- For Grade 3 hypertension not associated with symptoms, continue ramucirumab (or placebo) therapy with more intensive antihypertensive therapy. If systolic BP remains ≥160 mmHg or diastolic BP ≥100 mmHg for >2 weeks after initiation of additional antihypertensive therapy, hold ramucirumab (or placebo) while continuing appropriate antihypertensive therapy.
- If the hypertension is associated with symptoms, hold ramucirumab (or placebo) therapy until symptoms resolve and initiate antihypertensive therapy.
- If ramucirumab (or placebo) therapy is held for hypertension (that is, symptomatic hypertension, markedly elevated BP unresponsive to antihypertensive therapy), the dose of ramucirumab (or placebo) should be reduced upon retreatment to 6 mg/kg every 2 weeks. A second dose reduction to 5 mg/kg every 2 weeks should be undertaken if an additional postponement of therapy is required

Grade 4 or refractory

- 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 (systolic BP >160 mmHg or diastolic BP >100 mmHg for >4 weeks) despite appropriate oral medication (>2 oral agents at maximum tolerated dose) will be discontinued from ramucirumab. Treatment with paclitaxel may be continued if appropriate in the opinion of the investigator

9.4.2.1.3. Thromboembolic Events

Investigators should perform all testing required to fully characterize arterial or venous thromboembolic/vascular events. The incidence and type of thromboembolic/vascular events will be collected and reported.

Ramucirumab therapy should be discontinued in the event of any Grade 3/4 arterial thromboembolic event or any Grade 3/4 venous thromboembolic event 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 deep vein thrombosis or pulmonary embolism, or following a symptomatic deep vein thrombosis or pulmonary embolism when symptoms have resolved with the institution of anticoagulation therapy. Ramucirumab should also be

discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

9.4.2.1.4. Bleeding (Hemorrhagic) Events

Serious hemorrhagic AEs have been reported from clinical studies investigating ramucirumab. Hemorrhagic complications are associated with some malignancies (that is, variceal bleeding from portal hypertension in hepatocellular carcinoma, lower GI hemorrhage from bowel metastases in ovarian carcinoma) although the rate of these complications varies considerably. As detailed in the ramucirumab IB (Version 10.0 and subsequent versions), 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, although ongoing surveillance and identification (and exclusion) of patients with high bleeding risk remain essential and are detailed in the inclusion/exclusion criteria (Section 7).

9.4.2.1.5. Proteinuria

If, while on ramucirumab (or 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 (or placebo) therapy at the same dose without interruption. If the protein level is 2 to 3 g/24-hours, ramucirumab (or placebo) therapy will be held for 1 week and a 24-hour urine collection will be repeated. Ramucirumab (or placebo) treatment will resume at a reduced dose level (6 mg/kg every 2 weeks) once the protein level returns to <2 g/24-hours. A second dose reduction of ramucirumab (or placebo) to 5 mg/kg every 2 weeks is permitted if proteinuria ≥2 g/24-hours recurs. The patient will be discontinued from ramucirumab (or 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 2 weeks.

9.4.2.1.6. Gastrointestinal Perforation

Patients with unresected (or recurrent) primary tumors, 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 study entry are excluded from participation (Section 7.2). Ramucirumab DP should be permanently discontinued for patients who have experienced GI perforation.

9.4.2.1.7. Fistula Formation

Gastrointestinal and non-GI fistula formation has been associated with antiangiogenic agents including bevacizumab and sunitinib (Kamba and McDonald 2007). Some fistulas can be resolved with surgery procedures; however, fistulas can be fatal. The impact on the quality of life of having a fistula varies according to the location and extent of the fistula (Chen and Cleck 2009). A small number of fistula events have been reported in ramucirumab clinical trials.

Ramucirumab treatment should be discontinued in patients who develop fistulas.

9.4.2.1.8. Congestive Heart Failure in Patients Who Received Ramucirumab in Combination with Mitoxantrone or Following Prior Anthracycline Therapy

An increased risk of CHF has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously treated with anthracyclines or with other risk factors for CHF, including prior radiotherapy to the left chest wall. 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 preexisting 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 to 4 events consistent with CHF.

9.4.2.1.9. 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 or have undergone central venous access device placement within 7 days prior to randomization. Patients with postoperative and other nonhealing wound complications are excluded, as are patients for whom major surgical procedures are planned.

9.4.2.1.10. Liver Injury/Liver Failure

An independent data monitoring committee (IDMC) for the ramucirumab study CP12-0919 (I4T-IE-JVBF [JVBF]) (a randomized, blinded study evaluating ramucirumab versus placebo in hepatocellular carcinoma following prior sorafenib therapy) recommended modifications following a meeting on 02 August 2012. This 02 August 2012 meeting was the fifth meeting of the IDMC for this study (the prior meetings had concluded with recommendations to continue this study without modifications), and occurred at the request of the Sponsor to investigate a potential association of liver failure and other events of severe liver injury with ramucirumab.

The IDMC reviewed unblinded safety data from 400 patients who had been treated with either ramucirumab or placebo. The data cut-off date of this safety review was 18 July 2012.

In review of the safety data, the IDMC noted that death rates related to study medication were in the expected range for patients with hepatocellular carcinoma and cirrhosis. However, the IDMC observed a numeric imbalance of liver-related AEs, specifically for hepatic encephalopathy, between the 2 treatment arms. Based on this safety finding, the IDMC specifically addressed hepatic encephalopathy, hepatorenal syndrome, and ascites in the context of cirrhosis, exclusive of other etiologies of these diagnoses.

The IDMC recommended continuing the CP12-0919 study with modifications. These modifications included: (a) exclusion of patients with Child-Pugh B cirrhosis (or worse), (b) exclusion of patients with cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis, and (c) an additional criterion for discontinuation of study drug (ramucirumab or placebo) for patients with new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis. Although the CP12-0919 IDMC's recommendations are specific to the CP12-0919 study, ImClone Systems/Eli Lilly and Company (ImClone/Lilly) has chosen to implement these recommendations for ongoing ImClone/Lilly-sponsored studies in which patients are receiving investigational ramucirumab.

Ramucirumab should be discontinued following a new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

9.4.2.1.11. Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS) 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 the 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). has been associated with multiple clinical conditions including hypertensive encephalopathy, eclampsia, and renal failure with hypertension as well as the use of both immunosuppressive and cytotoxic drug (Hinchey et al. 1996; Marinella and Markert 2009). More recently, RPLS has been associated with the use of the anti-VEGF agent bevacizumab, as described in the prescribing information for this agent (Marinella and Markert 2009; Avastin package insert, 2011).

While the precise pathogenesis of RPLS has not been established, the pathophysiology may involve impaired cerebrovascular autoregulation leading to blood-brain barrier disruption and vasogenic edema (Schwartz 1996). Although the pathogenesis of RPLS appears to be

multifactorial, drug-induced endothelial damage and acute hypertension are frequently proposed causes of cerebrovascular dysfunction in RPLS (Garg 2001).

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

One SAE of RPLS has been reported in the double-blind, randomized, placebo-controlled, Phase 3 colorectal cancer study CP12-0920 (I4T-MC-JVBB [JVBB]). The event was determined to be related to administration of all study drugs, including blinded investigational DP (the treatment assignment for this patient remains blinded). Because hypertension is an identified risk for ramucirumab, investigators should control BP in accordance with the guidelines in Section 9.4.2.1.2. In addition, investigators should consider a diagnosis of RPLS in the setting of seizures, headache, nausea, delirium, visual changes, and/or other unexplained neurological symptoms, especially in combination with hypertension and MRI findings of hyperintensity on T2-weighted and fluid attenuated inversion recovery images. Ramucirumab DP should be permanently discontinued in patients with a confirmed diagnosis of RPLS.

9.4.3. General Dose Modifications: Paclitaxel

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 NCI-CTCAE, Version 4.03, 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.

9.4.3.1. Treatment Guideline and Dose Modification for Specific Adverse Events of Paclitaxel

9.4.3.1.1. Paclitaxel Hypersensitivity Reactions

In each case of hypersensitivity reaction associated with paclitaxel, the investigator should institute treatment measures according to the best available medical practice. The following treatment guidelines may be applicable:

For mild symptoms: Complete paclitaxel infusion. Supervise at bedside. No treatment required.

For moderate symptoms: Stop paclitaxel infusion. Administer diphenhydramine 25 to 50 mg IV and dexamethasone 8 to 20 mg IV (or equivalent, per institutional guidelines). Resume the paclitaxel infusion after recovery of symptoms at a reduced rate (20 mL/hour for 15 minutes). The infusion rate may then be increased to 40 mL/hour for 15 minutes, and subsequently at the full rate if symptoms do not recur. If symptoms recur, stop the paclitaxel infusion and remove patient from paclitaxel treatment.

For severe life-threatening symptoms: Stop paclitaxel infusion. Give IV diphenhydramine and dexamethasone (per institutional guidelines). Add epinephrine or bronchodilators if indicated. The patient should be removed from paclitaxel treatment.

9.5. Blinding

This is a randomized, double-blind, Phase 3 study. The randomization number will be assigned based on information obtained from the IWRS. Patients will be randomized to receive ramucirumab or matching placebo in a double-blind fashion such that neither the investigator, nor the patient, nor medical and ancillary medical staff, nor the Sponsor or its designees, will know which drug is being administered in addition to paclitaxel.

Ramucirumab and placebo for infusion will be identical in appearance in order to preserve blinding. In order to maintain this blind, study drug (ramucirumab or placebo) will be uniquely labeled and will be assigned to a patient by using IWRS.

9.5.1. 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 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.

9.5.2. 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. A double-blind study design is known to be imperfect in the oncolytic setting because the potential for individual unblinding exists due to treatment-related signs and symptoms. 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 therapy 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 for the patient to continue in the study.

9.6. 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 follow-up visit.

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this trial. 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. Nondrug supportive care procedures may be performed as medically necessary and appropriate in the opinion of the investigator. Appropriate management of hypersensitivity reactions is described in Section 9.4.2.1.2 (ramucirumab) and Section 9.4.3.1.1 (paclitaxel).

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment.

9.6.1. Antidiarrheal Agents

In the event of diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe (Grade 3 or 4) neutropenia, broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting must be hospitalized for IV hydration and correction of electrolyte imbalances.

9.6.2. Antiemetic Agents

The use of antiemetic agents is permitted at the discretion of the investigator.

9.6.3. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator. The chronic use of NSAIDs with a high risk of bleeding (for example, indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged 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 (for example, paracetamol/acetaminophen, metamizole, dipyrone, or propyphenazone) is acceptable.

9.6.4. Appetite Stimulants

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

9.6.5. Granulocyte-Colony Stimulating Factors

The protocol does not permit the routine use of colony-stimulating factors during treatment. The protocol does not allow the use of products that stimulate thrombopoiesis.

The use of granulocyte-colony stimulating factors is permitted during investigational therapy at the discretion of the investigator. Granulocyte-colony stimulating factors or similar agents are strongly recommended following Grade 3 or 4 neutropenia of duration >5 days or following any incidence of febrile neutropenia (ANC $<1.0 \times 10^9$/L with temperature $\geq$38.5°C).

9.6.6. Erythroid Growth Factors

The use of erythroid-stimulating factors (for example, erythropoietin) is permitted at the discretion of the investigator. Erythropoietic therapy may be considered for treatment of chemotherapy-induced anemia for patients; refer to American Society of Clinical Oncology and FDA guidelines (FDA 2007; Rizzo et al. 2008), or according to local guidelines.

9.7. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Treatment compliance is monitored by the review of drug accountability records (Section 9.1), and study medication administration data recorded in the patient's medical record and eCRF. The study medication will be administered only at the investigational sites by the authorized study personnel. As a result, treatment compliance is ensured.

A patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally missed more than 28 consecutive days of study medication (full doses) during the study. Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP before the final determination is made to discontinue the patient.

10. Efficacy, Patient-Reported Outcomes, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures related to efficacy, PROs, 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

Before the first dose of study drug, baseline tumor measurements will be performed on each patient. Computed tomography, including spiral CT scans, and MRIs are the preferred methods of measurement.

Investigators may collect PET scans for additional analyses, but PET scans will not be used as a method of response assessment. Bone scans may be performed if clinically indicated.

The method of assessment used at baseline must be used consistently for tumor assessment and will be repeated every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until radiographic documentation of PD.

The Sponsor or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study; if necessary, independent review of all scans may be considered following the completion of the study (Section 8.1.3).

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 without radiographical PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until radiographic documentation of PD, by the same method used at baseline and throughout the study. After the patient has radiographic disease progression, radiologic tests are no longer required and the patient will be followed up approximately every 8 weeks (+0 to 7 days) until the patient's death or overall study completion.

After patients have discontinued study treatment, they may receive additional anticancer therapy at the discretion of the investigator. The additional treatments should be documented on the CRF during the study period.

10.1.3. Primary Efficacy Measure

The primary efficacy measures are the duration of PFS and OS.

- **Progression-free survival** is measured from the date of randomization to the date of the first radiographically documented PD as defined by RECIST, Version1.1, or the date of death due to any cause, whichever is first. The censoring is taken in the following order:
  - if a patient does not have a complete baseline or post-baseline radiographic disease assessment, then the PFS will be censored at the date of randomization, regardless of whether or not radiographically determined disease progression or death has been observed for the patient; otherwise,
  - if a patient is alive and does not have radiographic progression as of the data-inclusion cut-off date, the PFS time will be censored at the date of the last adequate radiographic tumor assessment prior to cut-off date.
- **Overall survival** is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date, OS duration will be censored at the date of last known alive date prior to the data-inclusion cut-off date.

Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. The date of first documented radiographic disease progression must be recorded on the CRF even if it occurs after the patient has started a new therapy.

10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1). A responder is defined as any patient who exhibits an unconfirmed complete response (CR) or PR. Best response is determined from the sequence of responses assessed.

The following definitions for secondary efficacy measures will apply:

- **Time to progression** is defined as the time of randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1. For each patient who is not known to have had radiographic progression of disease as of the data-inclusion cut-off date, or who has died without radiographic progression of disease, TTP will be censored at the date of the patient's last radiographic tumor assessment prior to that cut-off date.
- **Objective response rate** is defined as the proportion of patients with a best overall response (BOR) of PR or CR. Patients who do not have a tumor response assessment for any reason are considered nonresponders and are included in the denominator when calculating the response rate. For each treatment arm, the number of patients achieving a response will be divided by the total of patients randomized to yield the proportion responding:

$$\text{ORR (\%)} = \frac{\text{\# of evaluable patients who have a best response of PR or CR}}{\text{\# of patients in analysis population}} \times 100$$

- **Duration of objective response** is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) to the date of the first radiographically documented PD as defined by RECIST, Version 1.1, or death due to any cause, whichever is first.

10.2. Health Outcome/Quality of Life Measures

10.2.1. Patient-Reported Outcomes

Disease-free, OS, and toxicity endpoints are typically included in oncology clinical trials to evaluate the effect of study treatment. Recently, however, inclusion of PROs has become routine as greater emphasis is placed on evaluating patient self-reports of the treatment benefit including the effect on symptoms and overall functioning or quality of life (QoL). These PRO measurements are intended to result in data useful to inform treatment decisions.

The assessment of QoL and health status endpoints will be conducted through use of the EORTC QLQ-C30 and the EQ-5D-3L questionnaires, respectively. The instruments should be administered together and in sequence order, with the EORTC QLQ-C30 presented first, followed by presentation of the EQ-5D-3L. Please refer to Section 8.1 for the specific timing of these assessments.

10.2.1.1. EORTC QLQ-C30

The EORTC QLQ-C30 is a self-administered, cancer-specific questionnaire with multidimensional scales (Aaronson et al. 1993). It consists of both multi-item scales and single-item measures, including 5 functional domains, a global QoL domain, 3 symptom domains, and 6 single items. Only patients for whom there is a validated translation in language in which the patient is fluent will complete the QLQ-C30.

10.2.1.2. EQ-5D-3L

The EQ-5D is a nonspecific and standardized instrument for use as a measure of self-reported health status. The EQ-5D 3 level version (EQ-5D-3L) was introduced in 1990 (EuroQol Group 1990). The EQ-5D-3L essentially consists of 2 pages - the EQ-5D descriptive system and the EQ visual analogue scale. The EQ-5D-3L descriptive system comprises 5 dimensions and each dimension has 3 levels. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. Additionally, patients will indicate their current health status by marking on a continuum ranging from 100 (best imaginable health state) to 0 (worst imaginable health state) (EuroQol Group 1990; Brooks et al. 1996). In 2014, investigators had validated EQ-5D-3L and generated a Chinese general population–based social value set using the time trade-off method (Liu et al. 2014).

10.3. 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 treatment before completing the study. The patient should be followed until the event is resolved,

stabilized, returned to baseline, until deemed irreversible, or otherwise explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.3.1. 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 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 AE 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. Any clinically significant findings from ECGs, laboratory assessments, vital sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

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 and up to 12 weeks following last study treatment dose should be reported immediately. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

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

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee. In addition, all AEs occurring after the patient receives the first dose of study treatment until 30 days after the decision is made to discontinue study treatment must be reported to the Sponsor or its designee via eCRF.

Any clinically significant findings from labs and vital sign measurements that result in a diagnosis should be reported to the Sponsor or its designee.

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

The investigator will decide whether he or she interprets the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug or 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, Version 4.03, will serve as a 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, Version 4.03, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim, the NCI-CTCAE term, and the NCI-CTCAE severity grade, AE verbatim text will also be mapped by the Sponsor or designee to corresponding terminology within Medical Dictionary for Regulatory Activities.

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.

10.3.1.1. Serious Adverse Events

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

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Initial or prolonged inpatient hospitalization
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason.

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

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

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

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with 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 therapy or other protocol-required procedure) should not be considered SAEs.

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

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 drug, 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.

10.3.1.2. 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 investigational product or study procedure. 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.

10.3.2. Safety Monitoring

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

Lilly will review SAEs within timeframes mandated by company procedures.

The Lilly CRP, will, as is appropriate, consult with the functionally independent GPS therapeutic area physician or clinical scientist, and review trends in safety data, laboratory analyses, and AEs:

- If a patient experiences elevated ALT ≥5× ULN and elevated total bilirubin ≥2× ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients

entering the study with ALT >3× ULN, monitoring should be triggered at ALT >2× baseline.

- Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 4.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only the GPS therapeutic area physician or clinical scientist can conduct additional analyses of the safety data.

For the purpose of this study, in which survival is a primary endpoint, all deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to assure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or other clinical AE is deemed serious, unexpected, and possibly related to study drug, only Lilly representatives external to the study team will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

10.3.3. Complaint Handling

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

Complaints related to unblinded comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs/devices 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 or 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 or she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

10.4.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria (Section 7) and to monitor patient health.

Attachment 1 lists the schedule for sample collections during study period. Attachment 2 summarizes all data required to be collected on the eCRF during the extension period (as defined in Section 8.1.4).

Attachment 3 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory. Standard laboratory tests, including hematology, coagulation, and urinalysis panels will be performed and analyzed by a local laboratory. Patient randomization and treatment decisions are based on local laboratory results only, unless the investigator chooses to use the central laboratory for such a purpose. Central laboratory results are used for study report purposes and where appropriate for safety analyses. Central laboratory samples should be collected even when local laboratory results are used to assess eligibility. A pregnancy test will be performed locally. For chemistry test, both central and local laboratory test should be performed at screening/baseline and prior to D1 of each treatment cycle. But only local laboratory test is required for chemistry test prior to D8 and D15 of each treatment cycle.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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.

10.4.2. Samples for Translational Research

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERB allow, a whole blood sample will be collected for pharmacogenetic analysis. This collection is a one-time whole blood collection that can be taken at any time during the study. However, it is recommended that the sample be collected before the first dose of study treatment.

Collection of samples for other biomarker research is also part of this study. Plasma and tumor tissue will be collected.

Required samples for translational research to be collected from all patients in this study are the following:

- Whole blood
- Plasma.

Optional samples for translational research that should be collected from patients in the study where possible are the following:

- Tumor tissues.

Attachment 5 lists the sampling schedule for translational research.

Whole blood samples will be stored and analysis may be performed on biomarker variants thought to play a role in endothelial cell proliferation, angiogenesis, ramucirumab mechanism of action, and/or cancer, which may include but not limited to VEGFR-2 and VEGF-A, to evaluate their association with clinical outcomes to ramucirumab. Polymorphisms in VEGF-A have been associated with OS and hypertension using other antiangiogenesis agents (Schneider et al. 2008).

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

Plasma will be stored and may be used for the analyses of various circulating factors related to the VEGF pathway and/or cancer; these factors may include, but not be limited to, levels of circulating VEGF-A, VEGF-B, VEGF-C, VEGF-D, placental growth factor (PlGF), soluble VEGFR-1, and soluble VEGFR-2, basic fibroblast growth factor (bFGF), and stromal cell-derived factor 1a (SDF1a).

Slides with unstained tumor sections or archived tissue blocks are required for biomarker research. Due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology reports accompanying archival tissue may also be requested.

Previously archived tumor tissue will be identified at baseline and designated for submission to the central laboratory. 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. After sectioning has been completed, the paraffin-embedded whole blocks will be returned to the investigator within 2 months. Slides will not be returned.

The tissue may be used to assess biomarkers that predict clinical outcome to treatment with ramucirumab. Mutations in VEGFR-2 have been identified in tumors and have been associated with VEGFR-2 expression and clinical outcome (Cerri et al. 2010; Yang et al. 2011). Such mutations may have an impact on ramucirumab binding and efficacy. This study may determine if these VEGFR-2 findings are relevant for gastric cancer and specifically for ramucirumab efficacy. Mutation profiling, copy number variability, gene expression, and

immunohistochemistry may be performed on tissue samples to determine an association between these biomarkers and ramucirumab efficacy.

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 them 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 drug.

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

10.5. Appropriateness of Measurements

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

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

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

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

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. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect PRO measures (for example, a rating scale), a daily dosing schedule, or an event diary.

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 study plan is to enroll approximately 450 patients with advanced gastric or GEJ adenocarcinoma after failure of any platinum and fluoropyrimidine doublet with or without anthracycline.

The approximately 450 patients will be randomized in a 2:1 ratio to Arm A (paclitaxel plus ramucirumab) and Arm B (paclitaxel plus placebo). Patients will be randomized using stratification factors ECOG PS (0 versus 1) and peritoneal metastatis (yes versus no).

Under the following assumptions:

- The randomization ratio is 2:1;
- OS in each arm follows exponential distribution;
- The OS hazard ratio for Arm A vs Arm B is 0.81;
- Control arm median OS = 10.5 months,

336 deaths (that is, 25% censoring rate) will provide at least 80% probability to assure that the effect size observed in this study is consistent with the global study, where effect size is defined by $\delta = \frac{1}{HR} - 1$. The above assurance probability is defined by $\text{Prob}\left[\hat{\delta}_{JVCR} > \rho\hat{\delta}_{JVBE}\right]$, where $\hat{\delta}_{JVBE}$=0.235 was estimated from the observed HR of 0.81 in the global study and $\hat{\delta}_{JVCR}$ will be estimated from the observed HR in this study. ρ is a constant set to 0.5, corresponding to 50% effect size retention from the global study.

Assuming further a constant accrual rate of 12 patients/month, it is estimated that the study will take approximately 44 months to obtain the required 336 deaths, with 37 months for accrual and 7 months for follow-up.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

Analyses of OS, PFS, and ORR will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to randomized treatment. Sensitivity analyses of the primary efficacy endpoints and other selected efficacy endpoints based on the per-protocol set (PPS) of patients may be performed if there are significant numbers of patients with major protocol violations. The PPS is defined as those patients in the ITT set who are compliant with the study protocol without major protocol violations. Safety will be analyzed for randomized patients receiving at least 1 dose of study treatment grouped by actual treatment received. Analyses of PROs will include

randomized patients that provide (for the instrument being analyzed) a baseline assessment and at least 1 postbaseline assessment; however, compliance will be based on the ITT population.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include:

- Summary of patients entered and randomized by country
- Total number of patients entered
- Total number of patients randomized, by treatment arm
- Summary of reasons for patients entered, but not randomized
- Total number of patients treated, by treatment arm
- Summary of reasons for patients randomly assigned but not treated.

A detailed summary of reasons for patient discontinuation from study treatment will be provided. A summary of all identified important protocol violations will be provided.

12.2.3. Patient Characteristics

Patient demographics, including the following, will be reported using descriptive statistics:

- Patient demographics
- Baseline disease characteristics
- Preexisting conditions
- Prior therapies
- Baseline factors.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

12.2.5. Treatment Compliance

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

12.2.6. Primary Outcome and Methodology

The co-primary efficacy objectives include evaluations of PFS and OS.

12.2.6.1. Progression-free Survival

The PFS is defined as the time from randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1, or death due to any cause, whichever is first.

Imaging will be performed every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD. Patients alive and without disease progression at data cut-off date or patients lost to follow-up will be censored at the day of their last adequate radiographic tumor assessment. If no baseline or post-baseline radiographic assessment is available, the patient will be censored at the date of randomization. If death or PD occurs after two or more consecutively missed radiographic visits, censoring will occur at the date of the last radiographic visit prior to the missed visits. The use of a new anticancer therapy prior to the occurrence of PD will result in censoring at the date of last adequate radiographic assessment prior to initiation of new therapy.

The primary analysis of PFS in this study will estimate the HR and its 2-sided 95% CI in a stratified Cox's proportional hazards model using treatment arm as a single covariate. The stratification factors included in the Cox model are the same as randomization strata. A sensitivity analysis with an unstratified Cox proportional hazards model will be employed. Stratified and unstratified log-rank tests will also be conducted.

The survival curves for each randomization arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% CIs for median PFS will be computed by the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982) using log-log-transformation. Survival rates at 6, 12, 18 and 24 months will also be estimated using KM estimates on the survival curve for each arm. Associated two-sided 95% CIs will also be calculated.

In addition, a multivariate Cox model will be used to adjust for baseline covariates because imbalances in potential prognostic factors could impact the analysis of survival. Covariates that are planned to be included are those prognostic factors identified in Study JVBE. Details of pre-specified covariates will be listed in the statistical analysis plan (SAP).

Additional sensitivity analyses for PFS using alternative censoring rules described in the SAP will be performed.

12.2.6.2. Overall Survival

Overall survival is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date, OS will be censored at the date of last known alive date prior to the data-inclusion cut-off date.

The analysis of OS will be conducted via similar methods for PFS, that is, stratified and unstratified Cox model and log-rank tests, KM curve, median estimates and survival rates with CI.

An interim OS analysis will be performed concurrently with the primary PFS analysis, and a final OS analysis will be performed if the primary objective is not achieved at interim.

12.2.7. Secondary Efficacy Analyses

Secondary efficacy endpoints include TTP, ORR and DOR.

Time to progression is defined as the time of randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1. For each patient who is not known to have had radiographic progression of disease as of the data-inclusion cut-off date, or who has died without radiographic progression, TTP will be censored at the date of the patient's last adequate radiographic tumor assessment prior to that cut-off date.

Time to progression will be analyzed using similar methods as described for PFS in Section 12.2.6. Additional sensitivity analyses for TTP using alternative censoring rules will be specified in the SAP.

Best overall response (BOR) will be determined using RECIST, Version 1.1. Objective response rate will be calculated as the number of patients who achieve a BOR of CR or PR, divided by the total number of patients randomized to the corresponding treatment arm (ITT analysis set). 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.

Objective response rate will be reported along with 2-sided 95% exact CIs using Clopper and Pearson's method for each treatment arm. The difference of ORR between 2 treatment arms will be evaluated using the Cochran-Mantel-Haenszel test adjusting for ECOG PS and peritoneal metastases.

Duration of objective response is measured from the time measurement criteria are first met for CR or PR (whichever is first) to the date of the first radiographically documented PD as defined by RECIST, v 1.1, or death due to any cause, whichever is first. Patients alive and without radiographic disease progression at data-inclusion cut-off date or patients lost to follow-up will be censored at the date of their last radiographic tumor assessment. DOR will be analyzed using KM method. Medians and their two-sided 95% CIs will be calculated.

12.2.8. Health Outcome/Quality of Life Analyses

Patient-reported outcome measures (that is, EORTC QLQ-C30 and EQ-5D-3L) data will be summarized by treatment arm using descriptive statistics including questionnaire compliance rates for the ITT population. Exploratory analyses may be performed to investigate associations between the PRO and clinical efficacy endpoints.

Following the EORTC guidelines (Fayers et al. 2001), the 30 items of the QLQ-C30 will be transformed into the 15 scales (1 global health status/QoL scale, 5 functional scales, and 9 symptoms scales/items). A linear transformation will be used to obtain scales ranging from 0 to 100, with a high score indicating a high level of functioning for the global and the functional scales and, conversely, a high level of symptomatology for the symptoms scales. Missing items within a scale will be handled according to the EORTC recommendations (Fayers et al. 2001). Scales will be presented using descriptive statistics.

The 5-dimension single-item 3-level EQ-5D-3L responses will be summarized using frequency distributions. The index score for the EQ-5D-3L will be calculated from a combination of responses using a weighting algorithm currently in development based on EQ-5D-3L Chinese validation study (EuroQol Group 1990; Brooks et al. 1996; Liu et al. 2014). The visual analog

scale is scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the patient's self-reported health during that day. The index score and the visual analog scale will be presented using summary statistics.

QoL scores and change from baseline will be summarized descriptively at each assessment time point by subtracting baseline scores for each individual from his or her own scores at the specific time point. The proportion of patients in each arm with deterioration in scores, improvement in scores, and stable scores at specific time points will be presented. Scores will be considered improved or deteriorated if change is ≥10 points (Osoba et al. 1998).

12.2.9. Safety Analyses

All safety summaries and analyses will be based upon the safety population as defined in Section 12.2.1.

Safety analyses will include summaries of the incidence of AEs by maximum NCI-CTCAE grade (Version 4.03) that occur during the study treatment period or within approximately 30 days after the decision is made for discontinuation from 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
- All hospitalizations and transfusions during the study treatment period or within 30 days after the decision is made to discontinue study treatment
- Selected concomitant medications, including growth factors (erythroid growth factors, granulocyte-colony stimulating factors, granulocyte-macrophage colony-stimulating factor), antiemetics, antihypertensive agents, and antibiotics, during the study treatment period or within 30 days after the decision is made to discontinue study treatment.

12.2.10. Subgroup Analyses

The following prespecified subgroup analyses are planned according to baseline characteristics. More subgroups may be provided in the SAP.

- Gender (males versus females)
- Age (<65 years versus ≥65 years)
- Ethnicity (Chinese versus non-Chinese)
- Eastern Cooperative Oncology Group PS (0 versus 1)
- Peritoneal metastases (yes versus no)
- Post discontinuation therapy use (yes versus no)
- Weight loss over the prior 3 months (≥10% versus <10%)
- Primary tumor location (gastric versus GEJ tumor)
- Time to progression on first-line therapy (<6 months versus ≥6 months)
- Presence of ascites (yes versus no)

- Pharmacodynamic biomarkers.

Cox models using treatment arm as a single covariate will be employed to estimate these HRs and CIs.

12.2.11. Statistical Analysis for Translational Research

Pharmacodynamic biomarker (that is, soluble VEGR-1 and VEGR-2; VEGF-A, VEGF-B, VEGF-C, and VEGF-D; PlGF, bFGF, and SDF1a) characteristics will be summarized by treatment arm. To explore the predictive features of biomarkers, subgroup analyses by these biomarkers will be performed for selected primary and secondary endpoints. For time-to-event variables such as OS and PFS, KM estimates will be generated by these biomarkers and Cox's proportional hazard models will be fitted including treatment-by-biomarker interactions. Objective response rate will be summarized by treatment and biomarkers.

12.2.12. Interim Analyses and Data Monitoring

The primary PFS analysis and an interim OS analysis will be reviewed by the Independent Data Monitoring Committee (IDMC) after at least 256 PFS events have been observed. The interim analysis will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies. The IDMC will be instructed to engage the Senior Management Designee (SMD), who may, if necessary, subsequently form an Internal Review Committee (IRC) to propose actions based upon the IDMC's recommendation. If the study shows early efficacy at interim (that is, both of the conditions described below are met), enrollment will be terminated and subjects randomized to the control arm may be permitted to cross over to the treatment arm under investigator discretion.

The primary objective will be claimed achieved if both of the following conditions are met:

(1) The point estimate of stratified HR for investigator-assessed OS is less than 1.
(2) The analysis of investigator-assessed PFS shows a one-sided, stratified p-value favoring Ramucirumab+paclitaxel arm less than 0.025.

If at least one of the conditions above are not met, the blinded study continues and a final OS analysis will apply. The final analysis will be conducted when approximately 336 OS events have been observed.

The unblinded interim analysis, including the efficacy and safety data, will be reviewed by the IDMC. Only the IDMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details are specified in the unblinding plan section of the SAP.

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 or where permitted by local law or regulation, by the patient's legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and 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.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

The study site's ERBs should be provided with the following:

- The current IB or package labeling (for example, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics) and updates during the course of the study
- Informed consent form
- Relevant curricula vitae.

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1. Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

2. The ICH GCP Guideline (E6)
3. 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 third-party organization.

An identification code assigned by the investigator 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.

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 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.

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Attachment 1. Protocol JVCR Study Schedule – Study Period

	Screening/Baseline (Prior to Randomization)				Treatment Period						Follow Up	
					Cycle 1, 2, 3... n (Repeat every 28 days ± 3 days)				Every 6 Wks (± 5d)	Every odd-numbered cycles	30 d Short-term F/U[a] (+ 0-7d)	Long-term F/U every 8 Wks (+ 0-7d)
Day	≤ 28d	≤ 21d	≤ 14d	≤ 7d	D1	D8	D15	D22				
Visit	0				1-n						801	802-8XX
Clinical Evaluations												
Informed Consent	X[b]											
Demography	X											
Medical History	X[c]											
Electrocardiogram[d]		X			X[e]					X[e]	X	
Echocardiogram/ MUGA		X[f]								X[f]	X	
ECOG Performance Status		X			X						X	
Concomitant Medication Assessment			X[g]		X	X	X				X	X[g]
Physical Exam, Height, and Weight			X[h]		X[h]						X[h]	
Vital Signs			X		X[i]	X[i]	X[i]				X	
Toxicity Assessments/AEs			X[c]		X	X	X				X	X[j]
PRO Assessment			X[k]		X[k]						X[k]	
Laboratory Evaluations												
Hematology Profile				X	X[l]	X[l]	X[l]				X	

	Screening/Baseline (Prior to Randomization)				Treatment Period						Follow Up	
					Cycle 1, 2, 3... n (Repeat every 28 days ± 3 days)				Every 6 Wks (± 5d)	Every odd-numbered cycles	30 d Short-term F/U[a] (+ 0-7d)	Long-term F/U every 8 Wks (+ 0-7d)
Day	≤ 28d	≤ 21d	≤ 14d	≤ 7d	D1	D8	D15	D22				
Visit	0				1-n						801	802-8XX
Coagulation Profile				X[s]						X[s]	X	
ALT, AST, Total Bilirubin (Local laboratory only)						X[m]	X[m]					
Full Serum Chemistry Profile (Both local and central laboratories)				X	X						X	
Urinalysis			X[n]		X[n]		X[n]				X[n]	
Pregnancy Test				X[o]						X[o]	X	
Efficacy Assessments												
Survival Information											X	X
Imaging/Tumor Assessments[d]		X							X[p]		X[q]	
Treatment Administration												
Administer Ramucirumab/ Placebo					X		X					
Administer Paclitaxel					X[r]	X	X[r]					

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; D/d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L = EuroQol-5 Dimension-3 Level Questionnaire; F/U = follow-up; IRR = infusion-related reaction; IWRS = interactive web response system; MUGA = multi-gated acquisition scan; PD = progressive disease; PRO = patient-reported outcome; SAE = serious adverse event; Wk = week; WOCBP = women of child-bearing potential.

[a] The short-term follow-up begins the day after the decision is made to discontinue study treatment and lasts approximately 30 days (no more than 37 days). If it is deemed to be in the best interest of the patient to start a new anti-cancer treatment prior to the scheduled end of the short-term follow-up visit, the follow-up visit duration may be shortened. In this case, the short-term follow-up assessments should be completed prior to the initiation of the new therapy.

[b] Written informed consent must be obtained prior to any study-related procedures or evaluations. Informed consent form signature alone does not define start of screening period, but first study-related procedure or evaluation date is to be used for IWRS call/date of screening visit.

[c] Any preexisting toxicity within 28 days prior to randomization should be documented and recorded as part of the medical history at baseline.

[d] Electrocardiogram and imaging will be performed locally.

[e] Additional ECGs will be collected within 3 days prior to the first infusion of Cycle 2, Cycle 3 and then every odd-numbered cycles. Thereafter, within 30 days after the discontinuation of chemotherapy, and within 30 days after the discontinuation of ramucirumab/placebo.

[f] To be performed at screening/baseline (within 21 days prior to randomization), within 3 days prior to the first infusion of Cycle 3 only, thereafter, within 30 days after the discontinuation of chemotherapy, and within 30 days after the discontinuation of ramucirumab/placebo.

[g] Assessment at baseline includes all medications taken within 28 days prior to randomization. Medication assessment during long-term follow up only collects information on any subsequent systemic anticancer therapy.

[h] Height measurements to be performed at screening/baseline only.

[i] To be obtained at every treatment visit, before and at the completion of each infusion of ramucirumab/placebo, and before and at the completion of chemotherapy administration. If paclitaxel is administrated within 30 minutes after the completion of ramuciumab/placebo infusion, the measurement of vital signs before paclitaxel administration is optional.

[j] All SAEs and all AEs considered at least possibly related to any study therapy will be followed until resolution, stabilization, return to baseline, or until deemed irreversible.

[k] To be completed within 3 days prior to the start of each cycle and at the short-term 30-day safety follow-up visit, before blood sampling or any extensive contact and consultation with the clinician/study investigator; such encounters may thereafter bias patient responses. The instruments should be administered together and in sequence order, with the EORTC QLQ-C30 presented first, followed by presentation of the EQ-5D-3L. Does not need to be completed prior to Cycle 1 if completed at screening/baseline.

[l] Hematology profile to be collected within 36 hours (blood may be collected the morning of study therapy or the day before, results to be available and evaluated prior to start of infusion) prior to treatment on Days 1, 8, and 15 of each cycle until discontinuation of paclitaxel and prior to the start (Day 1) of each 28-day cycle only thereafter (Arms A and B). Baseline lab assessments can be used for dosing for Cycle 1 Day 1 if performed within 7 days prior to Cycle 1 Day 1.

[m] ALT, AST, and total bilirubin to be collected within 36 hours (blood may be collected the morning of study therapy or the day before, results to be available and evaluated prior to start of infusion) prior to treatment on Days 1, 8, and 15 of each cycle until discontinuation of paclitaxel, prior to the start (Day 1) of each 28-day cycle thereafter (with full serum chemistry profile). Baseline lab assessments can be used for dosing for Cycle 1 Day 1 if performed within 7 days prior to Cycle 1 Day 1.

[n] Routine dipstick measurements and, if clinically indicated, microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection (to assess protein) must be obtained.

[o] Performed within 3 days prior to Day1 of every odd-numbered cycles. Or according to institutional guidelines (serum pregnancy test for WOCBP mandatory at baseline).

[p] Imaging studies and tumor assessments should be performed as scheduled every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD, even if therapy is delayed.

[q] For patients removed from the study due to symptomatic deterioration characterized as PD in the absence of radiographic documentation of PD.

[r] Paclitaxel must not be started earlier than 60 minutes after completion of the ramucirumab/placebo infusion. The 1-hour observation period between administration of ramucirumab/placebo and paclitaxel is mandatory for the first 2 cycles, but may be omitted in Cycle 3 and beyond, provided there has been no evidence of IRR

[s] Baseline lab assessments can be used for dosing for Cycle 1 Day 1 if performed within 7 days prior to Cycle 1 Day 1. Thereafter, performed within 3 days prior to treatment at Day 1 of every odd-numbered cycle. The coagulation profile test could be more often if clinically indicated.

Attachment 2. Protocol JVCR Study Schedule – Study Extension Period

Procedure[a]	Treatment Period in Extension Period (every cycle)	30-Day Short-Term Follow-Up[b] (+ 0-7d)
Visit	**501-5XX**	**901**
Toxicity Assessment/AEs	X	X
Administer Study Therapy	X	

Abbreviations: AE = adverse event; d = days.

[a] During the extension period, routine safety and efficacy monitoring, including radiographic evaluation of disease and laboratory testing, such as pregnancy testing, should be continued as necessary, and documentation retained within the source files, to confirm patient eligibility to continue on treatment or the 30-day short-term follow-up visit. The Sponsor will collect only data shown in this table for the extension period.

[b] The short-term follow-up begins the day after the decision is made to discontinue study treatment and lasts approximately 30 days (no more than 37 days).

Attachment 3. Protocol JVCR Clinical Laboratory Tests

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

Urinalysis[a]:
Routine dipstick measurements, and if clinically indicated, microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+ at evaluation, a 24-hour urine collection (to assess protein) must be obtained.

Coagulation Tests[a]:
Prothrombin time (PT/INR)
Partial thromboplastin time/activated Partial thromboplastin time (PTT/aPTT)

Clinical Chemistry[b,c]:
Serum Concentrations of:
Sodium
Potassium
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Alanine aminotranferase/serum glutamic pyruvic transaminase (ALT/SGPT)
Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT)
Blood urea nitrogen (BUN)
Creatinine
Uric acid
Calcium
Glucose, random
Albumin
Chloride
Total protein
Lactate dehydrogenase
Magnesium
Phosphorus

Serum Pregnancy Test (females only)[a]

Abbreviations: INR = international normalized ratio; IU = international units; L = liter; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by investigator-designated (local) laboratory.

[b] Assayed by sponsor-designated (central) laboratory and/or investigator-designated (local) laboratory.

[c] Patient randomization and treatment decisions are based on local laboratory results only, unless the investigator chooses to use the central laboratory for such a purpose. Central laboratory results are used for study report purposes and where appropriate for safety analyses. Central laboratory samples should be collected at screening/baseline and prior to D1 of each treatment cycle even when local laboratory results are used to assess eligibility and make treatment decisions.

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

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-Nuclear Antibody[a]**
AST	
GGT	**Anti-Smooth Muscle Antibody[a]**
CPK	

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

[a] Assayed by Lilly-designated central laboratory.

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

Attachment 5. Protocol JVCR Sampling Schedule for Translational Research

Procedure	Cycle 1 Preinfusion[a,b]	Cycle 2 Day 15[c] 4th ramucirumab/placebo infusion Preinfusion[b]	Cycle 4 Day 1[d] 7th ramucirumab/placebo infusion Preinfusion[b]	30-Day Short-Term Follow-Up[b] (+0-7 d)
Tumor tissue submission[e]	X			
Whole blood sample collection[f]	X			
Plasma sample collection	X	X	X	X[g]

Note: It is essential that the draw dates and draw times are accurately recorded.

Abbreviations: IRB = institutional review board.

[a] Prior to the first infusion. (It is recommended that this sample be taken after randomization and prior to administration of study treatment at Cycle 1.)

[b] Samples for plasma pharmacodynamic biomarkers: 1 tube.

[c] Approximately 6 weeks following the first infusion (that is, fourth infusion) of ramucirumab/placebo. Sampling applies only to patients receiving ramucirumab /placebo, excluding patients that discontinued ramucirumab/placebo.

[d] Approximately 12 weeks following the first infusion (that is, seventh infusion) of ramucirumab/placebo. Sampling applies only to patients receiving ramucirumab/placebo, excluding patients that discontinued ramucirumab/placebo.

[e] Collection of tumor tissue is optional in this study. Previously archived tumor tissue will be identified prior to randomization and designated for submission to the central laboratory.

[f] Unless precluded by local regulations or IRB policy, whole blood samples will be collected for pharmacogenetic analysis.

[g] If ramucirumab/placebo has to be discontinued, blood samples for plasma pharmacodynamic analysis has to be taken after 30 days (+0 to 7 days) of last ramucirumab/placebo infusion regardless if the paclitaxel administration is continuing.

Attachment 6. Protocol JVCR Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Source: Oken et al. 1982.

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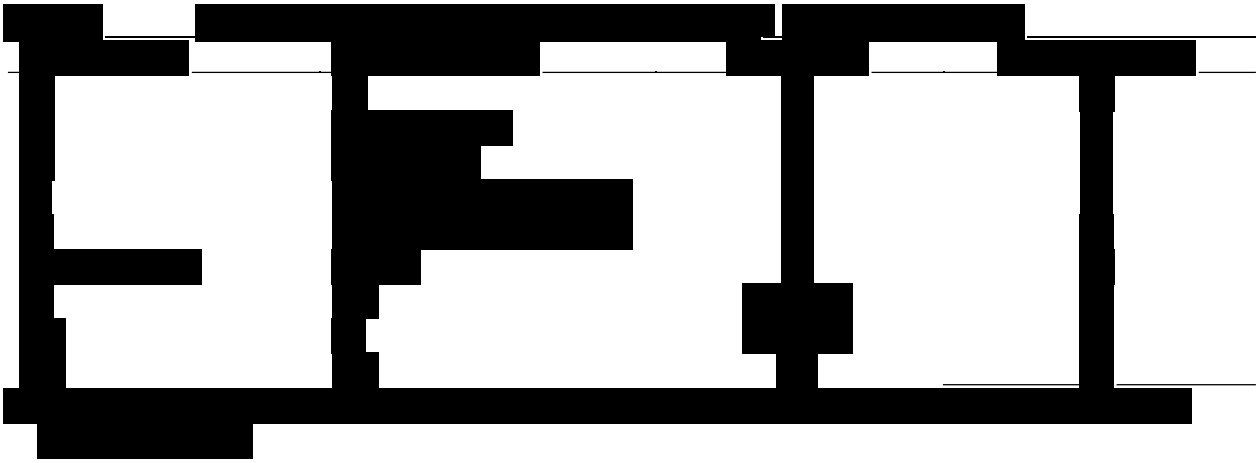

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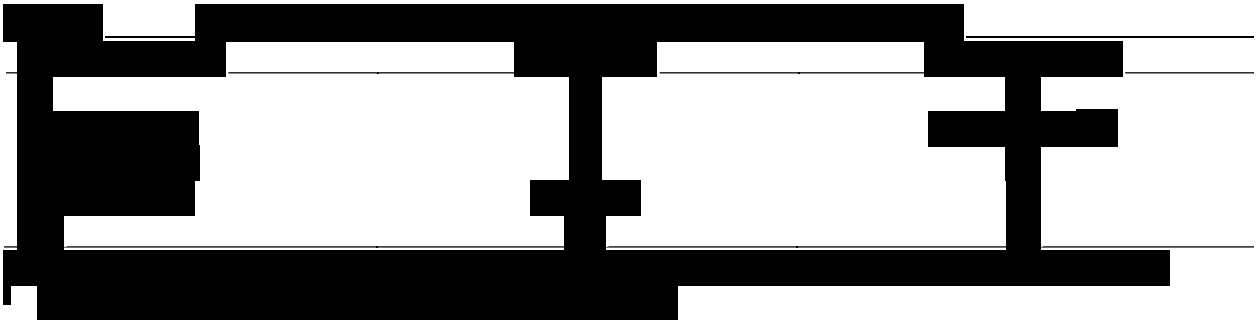

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Attachment 8. Protocol JVCR Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

-OR-

$$\text{GFR (mL/min/1.73m}^2) = 170 \times [\text{PCr}]^{-0.999} \times [\text{age}]^{-0.176}$$
$$\times [0.762 \text{ if patient is female}] \times [1.18 \text{ if patient is black}]$$
$$\times [\text{SUN}]^{-0.17} \times [\text{Alb}]^{+0.318}$$

Abbreviations: Alb = serum albumin, g/dL; CrCl = creatinine clearance; GFR = glomerular filtration rate; PCr = plasma creatinine, mg/dL; SUN = serum urea nitrogen, mg/dL; wt = weight.

Source: Murray and Ratain 2003.

Attachment 9. Protocol JVCR Amendment(c) Summary A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab (IMC-1121B) in Patients with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma, Refractory to or Progressive after First-Line Therapy with Platinum and Fluoropyrimidine

Overview

Protocol I4T-CR-JVCR (b) A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel with or without Ramucirumab (IMC-1121B) in Patients with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma, Refractory to or Progressive after First-Line Therapy with Platinum and Fluoropyrimidine 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:

- An interim analysis was added. Evaluation of PFS was added as a co-primary objectives along OS. Statistical assumptions and corresponding analysis plan were updated accordingly.
- Deleted the “follow up” and “study completion” in Figure JVCR 8.1, since the detailed information has been clarified in Figure JVCR 8.2.
- For the benefit of the patient, clarified crossover to the control arm may be permitted if the study show early efficacy at interim.
- Clarified the short-term follow-up procedure for subject initiating new anti-cancer therapy within this period.
- “Different drug product lots must not be mixed in a single infusion” was deleted, as Ramucirumab is commercial product and there is no such requirement.
- Clarified the treatment delay is at investigator discretion when AE/toxicities not listed in the protocol happened.
- To keep consistency with IB, “Fistula Formation” was added to “Treatment Guideline and Dose modification for Specific Adverse Events of Ramucirumab” and the following chapter numbers were updated.
- The footnotes e and f in attachment 1 are not applied for ECG and ECHO of V801, therefore they were deleted.

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~.
Additions have been identified by the use of underscore.

2. Synopsis

Number of Planned Patients:

Entered: 500
Randomized: 450
~~OS events: 336~~

Length of Study:

Planned first patient visit: November 2016
Planned last patient visit: July 2020
Planned interim analysis: An interim analysis is planned with a total of 256 PFS events

Objectives: The co-primary objective of this study is to evaluate PFS and OS in patients treated with paclitaxel plus ramucirumab (IMC 1121B) versus paclitaxel plus placebo as second-line treatment in patients with advanced gastric or GEJ adenocarcinoma after failure of any platinum and fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin).
The secondary objectives of the study are to evaluate:

- ~~PFS~~
- Time to progression
- Objective response rate
- Duration of objective response
- Safety profile
- Patient-reported outcome measures

In addition, exploratory objectives include:

- To explore biomarkers relevant to gastric or GEJ adenocarcinoma or safety, efficacy, and mechanism of action of ramucirumab.

Planned Duration of Treatment:

Long-term follow-up period (postdiscontinuation): After the decision is made to discontinue study treatment, follow-up information regarding further anticancer treatment and survival status will be collected at least every 8 weeks (+0 to 7 days). For patients who discontinue treatment for any reason other than radiographically documented PD (for example, symptomatic deterioration), information on disease progression (radiographic assessment) will also be collected until PD is documented by imaging. Follow-up will continue as long as the patient is alive, or until study completion ~~(336 deaths have occurred in the study)~~, whichever is first.

Criteria for Evaluation:

Efficacy:

Progression-free survival is defined as the time from the date of randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1, or death due to any cause, whichever is first.

Overall survival is defined as the time from the date of randomization to the date of death from any cause.

~~**Progression-free survival** is defined as the time from the date of randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1, or death due to any cause, whichever is first.~~

Statistical Methods:

Statistical:

Approximately 450 patients will be randomized to the 2 treatment arms in a 2:1 ratio (300 patients in Arm A [paclitaxel plus ramucirumab] and 150 patients in Arm B [paclitaxel plus placebo]) in order to obtain at least 336 deaths. Assuming an exponential distribution in each arm and a true underlying HR of 0.81 as observed in the global study, 336 deaths will provide at least 80% probability to assure that the effect size observed in this study is consistent with the global study. Also assuming a constant accrual rate of 12 patients/month, a median OS of 10.5 months in Arm B and a median OS of 13 months in Arm A, the study will take approximately 44 months to obtain the required 336 deaths (37 months for accrual and 7 months for the follow-up). The primary PFS analysis and an interim OS analysis will be performed when at least 256 PFS events have occurred.

Efficacy:

The ~~primary~~ analysis of ~~OS~~ PFS/OS in this study is to estimate the HR and its 2-sided 95% CIs in a stratified Cox's proportional hazards model using treatment arm as a single covariate. The stratification factors included in the Cox model are ECOG PS (0 versus 1) and peritoneal metastases (yes versus no). ~~An additional~~ A sensitivity analysis with an unstratified Cox proportional hazards model will be employed ~~to explore the effect of the stratification factor~~. Stratified (using the same stratification factor) and unstratified log-rank tests will also be conducted. The ~~OS~~ survival curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% CIs for median ~~OS~~ PFS/OS will be computed by the Brookmeyer and Crowley method. Landmark survival rates will also be estimated using KM estimates on the ~~OS~~ survival curve for each randomized arm. Associated 2-sided 95% CIs will also be calculated.

6. Objectives

6.1 Primary Objective

The co-primary objective of this study is to evaluate PFS and OS in patients treated with paclitaxel plus ramucirumab (IMC-1121B, LY3009806) versus paclitaxel plus placebo as second-line treatment in patients with advanced gastric or GEJ adenocarcinoma after failure of any platinum and fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin).

6.2 Secondary Objectives

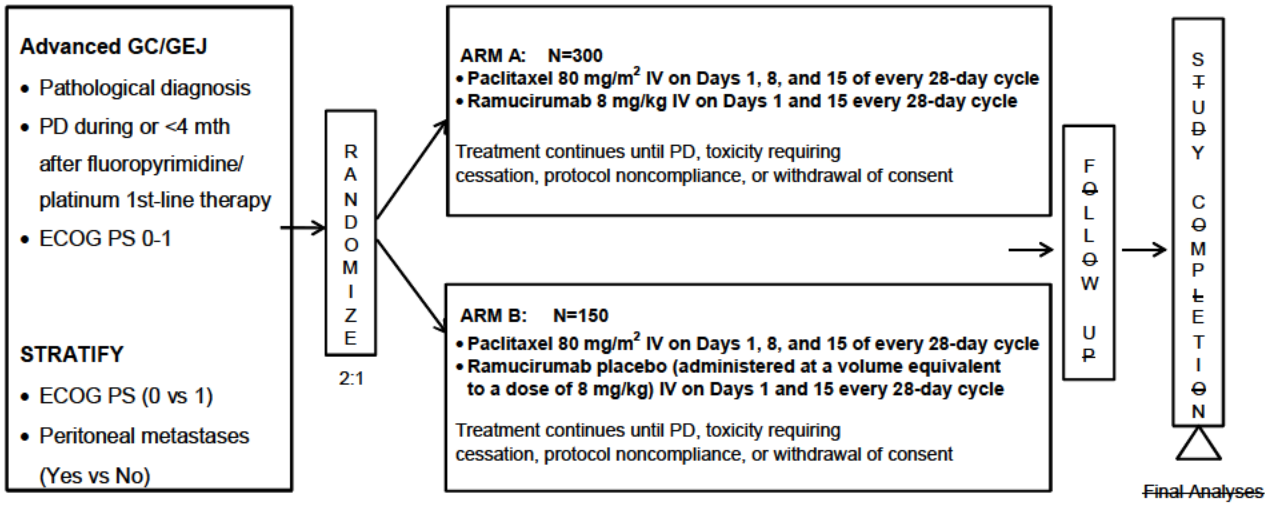
Secondary objectives are to evaluate:

- ~~PFS~~
- Time to progression (TTP)
- ORR
- Duration of objective response (DOR)
    - Safety profile
    - Patient-reported outcome (PRO) measures

8. Investigational Plan

8.1 Summary of Study Design

Figure JVCR 8.1 illustrates the study design.



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gastric cancer; GEJ = gastroesophageal junction adenocarcinoma; IV = intravenous; mth = months; N = number of patients; PD = progressive disease.

Figure JVCR 14.1. Illustration of study design for Study I4T-CR-JVCR.

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

- **Extension Period:** begins after study completion and ends at the end of trial. During the extension period, patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until one of the criteria for discontinuation is met. Crossover may be permitted to the control arm. The extension period includes extension period follow-up.
    - **Extension Period Follow-Up:** begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the extension period and lasts approximately 30 days (no more than 37 days).

8.1.2.1. Short-Term Follow-Up

For patients who discontinue treatment for reasons other than radiographic PD, imaging studies with tumor measurements/disease response assessments will continue to be performed every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD.

If it is deemed to be in the best interest of the patient to start a new anti-cancer treatment prior to the scheduled end of the short-term follow-up visit, the follow-up visit duration may be shortened. In this case, the short-term follow-up assessments should be completed prior to the initiation of the new therapy.

8.1.3. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the interim analysis (256 PFS events) if the study is stopped early, or following final analysies of OS (336 deaths; see Section 12) if the study is not stopped early, as determined by Lilly.

Investigators will continue to follow the Study Schedule for all patients until notified otherwise by Lilly.

Figure JVCR 8.2 provides an illustration of study completion, the extension period, and the end of trial.

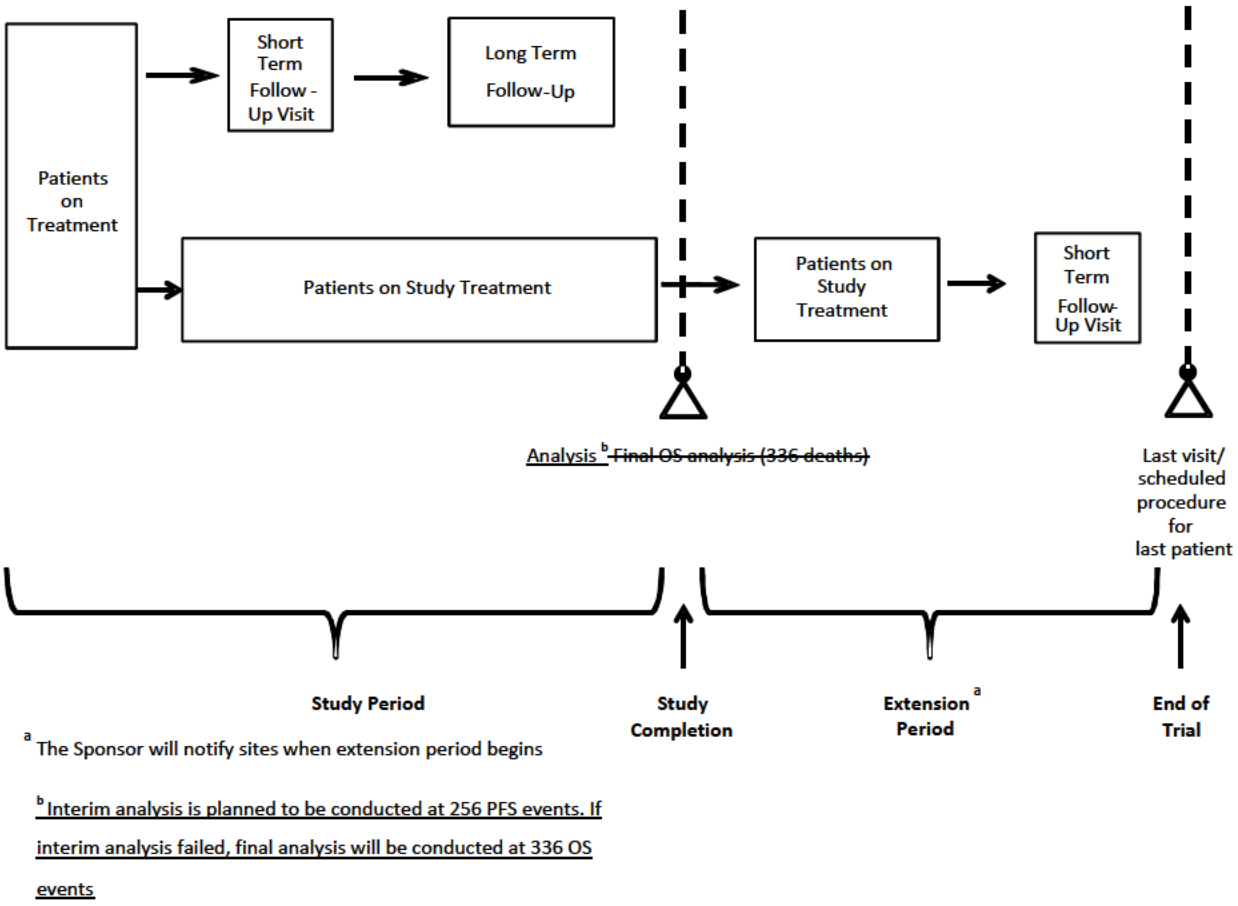


Figure JVCR 14.2. Study completion, the extension period, and the end of trial.

8.1.4. Extension Period

After study completion, all patients who are on study treatment and who are eligible for the extension period will be unblinded. Patients receiving study treatment and experiencing ongoing clinical benefit and no undue risks may continue to receive study treatment in the extension period until one of the criteria for discontinuation is met (Section 7.3). During the extension period, placebo will no longer be administered~~, and crossover will not be permitted~~. If the study shows early efficacy at interim (as defined in Section 12.2.12), or shows efficacy at final analysis, subjects randomized to the control arm may be permitted to crossover to the treatment arm under investigator discretion. Lilly will notify investigators when the extension period begins.

9. Treatment

9.1.2. Ramucirumab Drug Product or Placebo

Patients will receive ramucirumab/placebo via IV infusion over approximately 60 minutes. The infusion rate should not exceed 25 mg/minute. In the event that the infusion time takes longer

than 60 minutes (based on the patient's body weight), the infusion time should be accurately recorded on the eCRF. The first dose of ramucirumab (or placebo) is dependent upon the patient's screening/baseline body weight in kilograms. Subsequent doses of ramucirumab (or placebo) must be recalculated if there is a ≥10% change (increase or decrease) in body weight from the time of the most recent dose calculation; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in body weight from the time of the most recent dose calculation. 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 within 30 days prior to dose. If no recent dry weight is available, actual weight will be used.

~~Different drug product lots must not be mixed in a single infusion.~~

9.4.1.1.1. Requirements Prior to Day 1 of Each Treatment Cycle

Prior to Day 1 of each administration of study therapy, hematology, urine protein (dipstick), liver, and renal function must be adequate~~, and all toxicities (except for alopecia, venous thromboembolic events, hypertension, and proteinuria) must have resolved to Grade <2 or baseline. Preinfusion laboratory data may not be older than 36 hours. The following criteria in Table JVCR 9.1 and Table JVCR 9.2 must be fulfilled.~~ as required in Table JVCR 9.1 and Table JVCR 9.2. Preinfusion laboratory data may not be older than 36 hours. For AE/toxicities not listed in Table JVCR 9.1 and Table JVCR 9.2, treatment delay is at investigator discretion.

Table JVCR 14.1. Criteria for Paclitaxel Treatment on Day 1 of Each Cycle

Parameter	Criterion
Neutrophils	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥8 g/dL
Serum Creatinine	≤1.5× ULN or calculated creatinine clearance ≥50 ml/min
Bilirubin	≤1.5× ULN
AST/ALT	≤3× ULN if no liver metastases, ≤5× ULN if liver metastases
~~**Paclitaxel-related Toxicities/AEs**~~	~~NCI-CTCAE, Version 4.03, Grade <2 or baseline (except for alopecia)~~

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; min = minute; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

Table JVCR 14.2. Criteria for Ramucirumab Treatment on Day 1 of Each Cycle

Parameter	Criterion
Urine Protein	Dipstick <2+ or protein level <2 g/24-hr
~~**Ramucirumab-related Toxicities/AEs**~~ **Specific Adverse Event of Ramucirumab**	~~NCI-CTCAE, Version 4.03, Grade <2 or baseline (except for hypertension, venous thromboembolic events, and proteinuria)~~ Refer to 9.4.2.1

Abbreviations: AE = adverse event; hr = hour; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

9.4.1.1.2. Requirements Prior to Days 8 and 15 of Each Treatment Cycle

Prior to Days 8 and 15 of each administration of study therapy, hematology, urine protein (dipstick), and liver function must be adequate (see Table JVCR 9.3 and Table JVCR 9.4)~~, and all toxicities (except for alopecia, venous thromboembolic events, hypertension, and proteinuria) must have resolved to Grade <2 or baseline~~. Preinfusion laboratory data may not be older than 36 hours. For AE/toxicities not listed in Table JVCR 9.3 and Table JVCR 9.4, treatment delay is at investigator discretion.

Table JVCR 14.3. Criteria for Paclitaxel Treatment on Days 8 and 15 of Each Cycle

Parameter	Criterion
Absolute neutrophil count	≥1.0 × 10^9/L
Platelet count	≥75 × 10^9/L
Hemoglobin	≥8 g/dL
Bilirubin	≤1.5× ULN
AST/ALT	≤3× ULN if no liver metastases, ≤5× ULN if liver metastases
~~**Paclitaxel-related toxicities/AEs**~~	~~NCI-CTCAE, Version 4.03, Grade <2 or baseline (except for alopecia)~~

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

Table JVCR 14.4. Criteria for Ramucirumab Treatment on Day 15 of Each Cycle

Parameter	Criterion
Urine Protein	Dipstick <2+ or protein level <2 g/24-hr
~~**Ramucirumab-related Toxicities/AEs**~~ **Specific Adverse Event of Ramucirumab**	~~NCI-CTCAE, Version 4.03, Grade <2 or baseline (except for hypertension, venous thromboembolic events, and proteinuria)~~ Refer to 9.4.2.1

Abbreviations: AE = adverse event; hr = hour; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

9.4.2.1.7. Fistula Formation

Gastrointestinal and non-GI fistula formation has been associated with antiangiogenic agents including bevacizumab and sunitinib (Kamba and McDonald 2007). Some fistulas can be resolved with surgery procedures; however, fistulas can be fatal. The impact on the quality of life of having a fistula varies according to the location and extent of the fistula (Chen and Cleck 2009). A small number of fistula events have been reported in ramucirumab clinical trials.

Ramucirumab treatment should be discontinued in patients who develop fistulas.

~~9.4.2.1.7.~~ 9.4.2.1.8. Congestive Heart Failure in Patients Who Received Ramucirumab in Combination with Mitoxantrone or Following Prior Anthracycline Therapy

An increased risk of CHF has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously treated with anthracyclines or with other risk factors for CHF, including prior radiotherapy to the left chest wall. 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 preexisting 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 to 4 events consistent with CHF.

~~9.4.2.1.8.~~ 9.4.2.1.9. 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 or have undergone central venous access device placement within 7 days prior to randomization. Patients with postoperative and other nonhealing wound complications are excluded, as are patients for whom major surgical procedures are planned.

~~9.4.2.1.9.~~ 9.4.2.1.10. Liver Injury/Liver Failure

An independent data monitoring committee (IDMC) for the ramucirumab study CP12-0919 (I4T-IE-JVBF [JVBF]) (a randomized, blinded study evaluating ramucirumab versus placebo in hepatocellular carcinoma following prior sorafenib therapy) recommended modifications following a meeting on 02 August 2012. This 02 August 2012 meeting was the fifth meeting of the IDMC for this study (the prior meetings had concluded with recommendations to continue this study without modifications), and occurred at the request of the Sponsor to investigate a potential association of liver failure and other events of severe liver injury with ramucirumab. The IDMC reviewed unblinded safety data from 400 patients who had been treated with either ramucirumab or placebo. The data cut-off date of this safety review was 18 July 2012.

In review of the safety data, the IDMC noted that death rates related to study medication were in the expected range for patients with hepatocellular carcinoma and cirrhosis. However, the IDMC observed a numeric imbalance of liver-related AEs, specifically for hepatic encephalopathy, between the 2 treatment arms. Based on this safety finding, the IDMC specifically addressed hepatic encephalopathy, hepatorenal syndrome, and ascites in the context of cirrhosis, exclusive of other etiologies of these diagnoses.

The IDMC recommended continuing the CP12-0919 study with modifications. These modifications included: (a) exclusion of patients with Child-Pugh B cirrhosis (or worse), (b) exclusion of patients with cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis, and (c) an additional criterion for discontinuation of study drug (ramucirumab or placebo) for patients with new occurrence of

hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis. Although the CP12-0919 IDMC's recommendations are specific to the CP12-0919 study, ImClone Systems/Eli Lilly and Company (ImClone/Lilly) has chosen to implement these recommendations for ongoing ImClone/Lilly-sponsored studies in which patients are receiving investigational ramucirumab.

Ramucirumab should be discontinued following a new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

~~9.4.2.1.10.~~ 9.4.2.1.11. Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS) 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 the 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). has been associated with multiple clinical conditions including hypertensive encephalopathy, eclampsia, and renal failure with hypertension as well as the use of both immunosuppressive and cytotoxic drug (Hinchey et al. 1996; Marinella and Markert 2009). More recently, RPLS has been associated with the use of the anti-VEGF agent bevacizumab, as described in the prescribing information for this agent (Marinella and Markert 2009; Avastin package insert, 2011).

10 Efficacy, Patient-Reported Outcomes, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

10.1.3. Primary Efficacy Measure

The primary efficacy measure~~s is~~ are the duration of PFS and OS.

- **Progression-free survival** is measured from the date of randomization to the date of the first radiographically documented PD as defined by RECIST, Version1.1, or the date of death due to any cause, whichever is first. The censoring is taken in the following order:
  - if a patient does not have a complete baseline or post-baseline radiographic disease assessment, then the PFS will be censored at the date of randomization, regardless of whether or not radiographically determined disease progression or death has been observed for the patient; otherwise,
  - if a patient is alive and does not have radiographic progression as of the data-inclusion cut-off date, the PFS time will be censored at the date of the last adequate radiographic tumor assessment prior to cut-off date.

- **Overall survival** is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date, OS duration will be censored at the date of last known alive date prior to the data-inclusion cut-off date.

Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. The date of first documented radiographic disease progression must be recorded on the CRF even if it occurs after the patient has started a new therapy.

10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1). A responder is defined as any patient who exhibits an unconfirmed complete response (CR) or PR. Best response is determined from the sequence of responses assessed.

The following definitions for secondary efficacy measures will apply:

- ~~**Progression-free survival** is measured from the date of randomization to the date of the first radiographically documented PD as defined by RECIST, Version1.1, or the date of death due to any cause, whichever is first. The censoring is taken in the following order:~~
  - ~~if a patient does not have a complete baseline or post-baseline radiographic disease assessment, then the PFS will be censored at the date of randomization, regardless of whether or not radiographically determined disease progression or death has been observed for the patient; otherwise,~~
  - ~~if a patient is alive and does not have radiographic progression as of the data-inclusion cut-off date , the PFS time will be censored at the date of the last adequate radiographic tumor assessment.~~
- **Time to progression** is defined as the time of randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1. For each patient who is not known to have had radiographic progression of disease as of the data-inclusion cut-off date, or who has died without radiographic progression of disease, TTP will be censored at the date of the patient's last radiographic tumor assessment prior to that cut-off date.
- **Objective response rate** is defined as the proportion of patients with a best overall response (BOR) of PR or CR. Patients who do not have a tumor response assessment for any reason are considered nonresponders and are included in the denominator when calculating the response rate. For each treatment arm, the number of patients achieving a response will be divided by the total of patients randomized to yield the proportion responding:

$$\text{ORR (\%)} = \frac{\text{\# of evaluable patients who have a best response of PR or CR}}{\text{\# of patients in analysis population}} \times 100$$

- **Duration of objective response** is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) to the date of the first radiographically documented PD as defined by RECIST, Version 1.1, or death due to any cause, whichever is first.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The study plan is to enroll approximately 450 patients with advanced gastric or GEJ adenocarcinoma after failure of any platinum and fluoropyrimidine doublet with or without anthracycline.

The approximately 450 patients will be randomized in a 2:1 ratio to Arm A (paclitaxel plus ramucirumab) and Arm B (paclitaxel plus placebo). Patients will be randomized using stratification factors ECOG PS (0 versus 1) and peritoneal metastatis (yes versus no).

Under the following assumptions:

- The randomization ratio is 2:1;
- OS in each arm follows exponential distribution;
- The OS hazard ratio for Arm A vs Arm B is 0.81;
- Control arm median OS = 10.5 months.

~~The primary objective of this study is to evaluate the OS in patients treated with Arm A (paclitaxel plus ramucirumab) versus Arm B (paclitaxel plus placebo) as second-line treatment in patients with advanced gastric or GEJ adenocarcinoma after failure of any platinum and fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin). The study will randomize approximately 450 patients in a 2:1 ratio (300 patients in Arm A and 150 patients in Arm B). The primary analysis will be performed after 336 deaths have occurred (that is, a 25% censoring rate). Assuming an exponential distribution in each arm and a true underlying HR of 0.81 as observed in the global Study JVBE,~~ 336 deaths (that is, 25% censoring rate) will provide at least 80% probability to assure that the effect size observed in this study is consistent with the global study, where effect size is defined by $\delta = \frac{1}{HR} - 1$. The above assurance probability is defined by $\text{Prob}\lfloor \hat{\delta}_{JVCR} > \rho\hat{\delta}_{JVBE} \rfloor$, where $\hat{\delta}_{JVBE}$ =0.235 was estimated from the observed HR of 0.81 in the global study and $\hat{\delta}_{JVCR}$ will be estimated from the observed HR in this study. ρ is a constant set to 0.5, corresponding to 50% effect size retention from the global study.

Assuming further a constant accrual rate of 12 patients/month, it is estimated that ~~a median OS of 10.5 months in Arm B and a median OS of 13 months in Arm A,~~ the study will take approximately 44 months to obtain the required 336 deaths, with ~~(~~37 months for accrual and 7 months for ~~the~~ follow-up~~)~~.

12.2.6. Primary Outcome and Methodology

~~Overall survival is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data inclusion cut-off date, OS will be censored at the date of last known alive date prior to the data inclusion cut-off date.~~

~~The primary analysis of OS in this study will estimate the HR and its 2-sided 95% CIs in a stratified Cox's proportional hazards model using treatment arm as a single covariate. The stratification factors included in the Cox model are ECOG PS (0 versus 1) and peritoneal metastases (yes versus no). An additional analysis with an unstratified Cox proportional hazards model will be employed to explore the impact of the stratification factor. Stratified (using the same stratification factor) and unstratified log-rank tests will also be conducted.~~

~~The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% CIs for median OS will be computed by the Brookmeyer and Crowley method. Survival rates at 6, 12, 18 and 24 months will also be estimated using KM estimates on the OS curve for each randomized arm. Associated two-sided 95% CIs will also be calculated.~~

~~In addition, a multivariate Cox model will be used to adjust for baseline covariates as small imbalances in potential prognostic factors could impact the analysis of survival. Covariates that are planned to be included are those prognostic factors identified in Study JVBE. Details of pre-specified covariates will be listed in the statistical analysis plan (SAP).~~

~~The final efficacy analysis will be performed when at least 336 deaths are observed. No interim analysis is planned.~~

The co-primary efficacy objectives include evaluations of PFS and OS.

12.2.6.1. Progression-free Survival

The PFS is defined as the time from randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1, or death due to any cause, whichever is first.

Imaging will be performed every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD. Patients alive and without disease progression at data cut-off date or patients lost to follow-up will be censored at the day of their last adequate radiographic tumor assessment. If no baseline or post-baseline radiographic assessment is available, the patient will be censored at the date of randomization. If death or PD occurs after two or more consecutively missed radiographic visits, censoring will occur at the date of the last radiographic visit prior to the missed visits. The use of a new anticancer therapy prior to the occurrence of PD will result in censoring at the date of last adequate radiographic assessment prior to initiation of new therapy.

The primary analysis of PFS in this study will estimate the HR and its 2-sided 95% CI in a stratified Cox's proportional hazards model using treatment arm as a single covariate. The stratification factors included in the Cox model are the same as randomization strata. A sensitivity analysis with an unstratified Cox proportional hazards model will be employed. Stratified and unstratified log-rank tests will also be conducted.

The survival curves for each randomization arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% CIs for median PFS will be computed by the

Brookmeyer and Crowley method (Brookmeyer and Crowley 1982) using log-log-transformation. Survival rates at 6, 12, 18 and 24 months will also be estimated using KM estimates on the survival curve for each arm. Associated two-sided 95% CIs will also be calculated.

In addition, a multivariate Cox model will be used to adjust for baseline covariates because imbalances in potential prognostic factors could impact the analysis of survival. Covariates that are planned to be included are those prognostic factors identified in Study JVBE. Details of pre-specified covariates will be listed in the statistical analysis plan (SAP).

Additional sensitivity analyses for PFS using alternative censoring rules described in the SAP will be performed.

12.2.6.2. Overall Survival

Overall survival is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date, OS will be censored at the date of last known alive date prior to the data-inclusion cut-off date.

The analysis of OS will be conducted via similar methods for PFS, that is, stratified and unstratified Cox model and log-rank tests, KM curve, median estimates and survival rates with CI.

An interim OS analysis will be performed concurrently with the primary PFS analysis, and a final OS analysis will be performed if the primary objective is not achieved at interim.

12.2.7. Secondary Efficacy Analyses

Secondary efficacy endpoints include ~~PFS,~~ TTP, ORR and DOR.

~~The PFS is defined as the time from randomization to the date of the first radiographically documented PD as defined by RECIST, Version 1.1, or death due to any cause, whichever is first. Imaging will be performed every 6 weeks (±5 days) following the first dose of study therapy for the first 6 months, and every 9 weeks (±5 days) thereafter, until documentation of radiographic PD. The primary censoring rules are the following:~~

- ~~if a patient does not have a complete baseline or post-baseline radiographic disease assessment, then the PFS will be censored at the date of randomization, regardless of whether or not radiographically determined disease progression or death has been observed for the patient; otherwise,~~
- ~~if a patient is alive and does not have radiographic progression as of the data-inclusion cut-off date, the PFS time will be censored at the date of the last adequate radiographic tumor assessment.~~

~~The analysis of PFS distributions in the two treatment arms will be conducted via similar methods as described in Section 12.2.6. Additional sensitivity analyses for PFS using alternative censoring rules will be specified in the SAP.~~

~~Progression-free survival final analysis will be conducted concurrently with OS final analysis when at least 336 deaths have occurred. It is projected that approximately 430 PFS events would have occurred at that time assuming an exponential distribution for each arm and median PFS times of 4.35 months and 3 months for Arm A and Arm B, respectively (HR=0.69), for which it will provide at least 95% power assuming a two-sided alpha of 0.05.~~

Time to progression is defined as the time of randomization to the date of the first radiographically documented PD as defined by RECIST, Version1.1. For each patient who is not known to have had radiographic progression of disease as of the data-inclusion cut-off date, or who has died without radiographic progression, TTP will be censored at the date of the patient's last adequate radiographic tumor assessment prior to that cut-off date.

Time to progression will be analyzed ~~at the same time of the final analysis for OS~~ using similar methods as described for ~~OS~~ PFS in Section 12.2.6. Additional sensitivity analyses for TTP using alternative censoring rules will be specified in the SAP.

Best overall response (BOR) will be determined using RECIST, Version 1.1. Objective response rate will be calculated as the number of patients who achieve a BOR of CR or PR, divided by the total number of patients randomized to the corresponding treatment arm (ITT analysis set). 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.

Objective response rate will be reported along with 2-sided 95% exact CIs using Clopper and Pearson's method for each treatment arm. The difference of ORR between 2 treatment arms will be evaluated using the Cochran-Mantel-Haenszel test adjusting for ECOG PS and peritoneal metastases. ~~Analyses will be conducted at the same time of the final analysis for OS.~~

Duration of objective response is measured from the time measurement criteria are first met for CR or PR (whichever is first) to the date of the first radiographically documented PD as defined by RECIST, v 1.1, or death due to any cause, whichever is first. Patients alive and without radiographic disease progression at data-inclusion cut-off date or patients lost to follow-up will be censored at the date of their last radiographic tumor assessment. DOR will be analyzed using KM method. Medians and their two-sided 95% CIs will be calculated. ~~Analyses will be conducted at the same time of the final analysis for OS.~~

~~12.2.12. 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.~~

12.2.12. Interim Analyses and Data Monitoring

The primary PFS analysis and an interim OS analysis will be reviewed by the Independent Data Monitoring Committee (IDMC) after at least 256 PFS events have been observed. The interim analysis will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies. The IDMC will be instructed to engage the Senior Management Designee (SMD), who may, if necessary, subsequently form an Internal

Review Committee (IRC) to propose actions based upon the IDMC's recommendation. If the study shows early efficacy at interim (that is, both of the conditions described below are met), enrollment will be terminated and subjects randomized to the control arm may be permitted to cross over to the treatment arm under investigator discretion.

The primary objective will be claimed achieved if both of the following conditions are met:

(1) The point estimate of stratified HR for investigator-assessed OS is less than 1.

(2) The analysis of investigator-assessed PFS shows a one-sided, stratified p-value favoring Ramucirumab+paclitaxel arm less than 0.025.

If at least one of the conditions above are not met, the blinded study continues and a final OS analysis will apply. The final analysis will be conducted when approximately 336 OS events have been observed.

The unblinded interim analysis, including the efficacy and safety data, will be reviewed by the IDMC. Only the IDMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details are specified in the unblinding plan section of the SAP.

Attachment 1. Protocol JVCR Study Schedule – Study Period

	Screening/Baseline (Prior to Randomization)				Treatment Period						Follow Up	
					Cycle 1, 2, 3... n (Repeat every 28 days ± 3 days)				Every 6 Wks (± 5d)	Every odd-numbered cycles	30 d Short-term F/U[a] (+ 0-7d)	Long-term F/U every 8 Wks (+ 0-7d)
Day	≤ 28d	≤ 21d	≤ 14d	≤ 7d	D1	D8	D15	D22				
Visit	0				1-n						801	802-8XX
Clinical Evaluations												
Informed Consent	X[b]											
Demography	X											
Medical History	X[c]											
Electrocardiogram[d]		X			X[e]					X[e]	X[e]	
Echocardiogram/ MUGA		X[f]								X[f]	X[f]	
ECOG Performance Status		X			X						X	
Concomitant Medication Assessment			X[g]		X	X	X				X	X[g]
Physical Exam, Height, and Weight			X[h]		X[h]						X[h]	
Vital Signs			X		X[i]	X[i]	X[i]				X	
Toxicity Assessments/AEs			X[c]		X	X	X				X	X[j]
PRO Assessment			X[k]		X[k]						X[k]	
Laboratory Evaluations												
Hematology Profile				X	X[l]	X[l]	X[l]				X	

	Screening/Baseline (Prior to Randomization)				Treatment Period						Follow Up	
					Cycle 1, 2, 3... n (Repeat every 28 days ± 3 days)				Every 6 Wks (± 5d)	Every odd-numbered cycles	30 d Short-term F/U[a] (+ 0-7d)	Long-term F/U every 8 Wks (+ 0-7d)
Day	≤ 28d	≤ 21d	≤ 14d	≤ 7d	D1	D8	D15	D22				
Visit	0				1-n						801	802-8XX
Coagulation Profile				X[s]						X[s]	X	
ALT, AST, Total Bilirubin (Local laboratory only)						X[m]	X[m]					
Full Serum Chemistry Profile (Both local and central laboratories)				X	X						X	
Urinalysis			X[n]		X[n]		X[n]				X[n]	
Pregnancy Test				X[o]						X[o]	X	
Efficacy Assessments												
Survival Information											X	X
Imaging/Tumor Assessments[d]		X							X[p]		X[q]	
Treatment Administration												
Administer Ramucirumab/ Placebo					X		X					
Administer Paclitaxel					X[r]	X	X[r]					

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; D/d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L = EuroQol-5 Dimension-3 Level Questionnaire; F/U = follow-up; IRR = infusion-related reaction; IWRS = interactive web response system; MUGA = multi-gated acquisition scan; PD = progressive disease; PRO = patient-reported outcome; SAE = serious adverse event; Wk = week; WOCBP = women of child-bearing potential.

[a] The short-term follow-up begins the day after the decision is made to discontinue study treatment and lasts approximately 30 days (no more than 37 days). If it is deemed to be in the best interest of the patient to start a new anti-cancer treatment prior to the scheduled end of the short-term follow-up visit, the follow-up visit duration may be shortened. In this case, the short-term follow-up assessments should be completed prior to the initiation of the new therapy.

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