I4T-MC-JVDE Protocol (c)

Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ramucirumab and Best Supportive Care (BSC) Versus Placebo and BSC as Second-Line Treatment in Patients With Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-Line Therapy With Sorafenib

NCT02435433

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1. Protocol I4T-MC-JVDE(c) Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ramucirumab and Best Supportive Care (BSC) Versus Placebo and BSC as Second-Line Treatment in Patients With Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-Line Therapy With Sorafenib

Ramucirumab (LY3009806)

Study JVDE is a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study evaluating the efficacy and safety of ramucirumab as a single agent for the treatment of patients with advanced HCC and elevated baseline AFP after intolerance or progression on prior sorafenib therapy.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
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Approval Date: 24-Apr-2017 GMT

2. Synopsis

Study Rationale

Results of the global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study I4T-IE-JVBF (REACH) support the hypothesis that ramucirumab treatment may provide meaningful benefits for patients with advanced hepatocellular carcinoma (HCC) after prior sorafenib therapy. REACH demonstrated a numerical improvement in overall survival, though this benefit was not statistically significant. Robust improvement in progression-free survival, time to progression, and objective response rate was observed in the ramucirumab arm compared with the placebo arm. The efficacy results are supported by sensitivity analyses and subgroup analyses.

In preplanned and exploratory analyses of REACH, ramucirumab treatment led to a progressively greater reduction in the risk of death (that is, a more favorable hazard ratio) in patients with progressively higher baseline alpha-fetoprotein (AFP) values.

The REACH results show that ramucirumab has activity and a manageable safety profile in HCC patients with elevated baseline AFP. Given the number of agents that have failed in HCC clinical trials, selection of patients will likely be required for any new agents to demonstrate a survival benefit. For ramucirumab, patients with a baseline AFP ≥400 ng/mL derived survival benefit in REACH, and the survival benefit from ramucirumab treatment in this selected patient population with an elevated baseline AFP will be assessed in this trial JVDE.

Clinical Protocol Synopsis: Study I4T-MC-JVDE

Name of Investigational Product: Ramucirumab (LY3009806)	
Title of Study: Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ramucirumab and Best Supportive Care (BSC) Versus Placebo and BSC as Second-Line Treatment in Patients With Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-Line Therapy With Sorafenib	
Number of Planned Patients: Entered: 465 Enrolled/Randomized: 279	**Phase of Development:** 3
Length of Study: approximately 32 months Planned first patient visit: June 2015 Planned last patient visit: January 2018 Planned interim analysis: when approximately 50 and 150 patients have received 3 cycles of study treatment, died, or discontinued study treatment; thereafter, twice per year.	
Objectives: The primary objective of this study is to compare overall survival (OS) for ramucirumab versus placebo in patients with advanced hepatocellular carcinoma (HCC) after intolerance or progression on prior sorafenib treatment. The secondary objectives of the study are to evaluate: progression-free survival, time to radiographic progression, objective response rate (ORR), safety profile of ramucirumab, ramucirumab pharmacokinetics, immunogenicity of ramucirumab, time to deterioration in Eastern Cooperative Group performance status (ECOG PS), time to deterioration in Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8), and other patient-reported outcome measures of disease-specific symptoms and health-related quality of life. The exploratory objective of the study is to explore biomarkers relevant to ramucirumab, angiogenesis, and the disease state and to correlate these markers to clinical outcome.	
Study Design: Study JVDE is a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study evaluating the efficacy and safety of ramucirumab as a single agent for the treatment of patients with advanced HCC and elevated baseline AFP after intolerance or progression on prior sorafenib therapy. Study treatment will be administered by study site personnel in an outpatient setting.	
Diagnosis and Main Criteria for Inclusion and Exclusions: Eligible patients are required to have a diagnosis of HCC based on (1) histopathologic or cytologic findings or (2) in the absence of histologic confirmation, a diagnosis of cirrhosis and HCC with classical imaging characteristics. Patients must have received prior sorafenib as the only systemic therapeutic intervention for advanced HCC; duration of sorafenib treatment must have been at least 14 days, and patients must have discontinued sorafenib ≥14 days prior to randomization. Patients also must have (1) experienced radiographically confirmed disease progression during or after discontinuation of sorafenib therapy or (2) discontinued sorafenib because of intolerance despite appropriate sorafenib management and supportive care. Additional requirements include Child-Pugh score of <7 (Child-Pugh Class A only); Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease not amenable or refractory to locoregional therapy, AFP ≥400 ng/mL, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Patients of either sex are eligible if they are ≥18 years of age or of an age acceptable according to local regulations, whichever is older. Patients with any of the following are not eligible: previous or current hepatic encephalopathy or clinically meaningful ascites; ongoing or recent hepatorenal syndrome; prior liver transplant; hepatic locoregional therapy after treatment with sorafenib.	
Test Product, Dosage, and Mode of Administration: Ramucirumab 8 mg/kg administered as an intravenous infusion on Day 1 of each 14-day cycle.	
Reference Therapy, Dose, and Mode of Administration: Placebo (equivalent volume) administered as an intravenous infusion on Day 1 of each 14-day cycle.	

Planned Duration of Treatment: A treatment cycle is defined as a period of 14 days. Patients will continue to receive study treatment until radiographic or clinical progression of disease or until another criterion for discontinuation is met.

Short-term follow-up (postdiscontinuation): approximately 30 days (±7) days

Long-term follow-up (postdiscontinuation): until death or study completion, whichever occurs first

Criteria for Evaluation:

Efficacy: Overall survival will be 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 cutoff date for OS analysis, OS will be censored on the last date the patient is known to be alive.

Progression-free survival is defined as time from the date of randomization to the date of first observation of objective progression or death from any cause.

Time to radiographic progression is defined as the time from the date of randomization to the date of first observation of objective progression.

Objective response rate is defined as the percentage of patients who achieve a best overall response of complete response or partial response. Best overall response will be classified based on the overall responses assessed by study investigators according to Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1.

Time to deterioration in ECOG PS is defined as the time from the date of randomization to the first date observing ECOG PS ≥2 (that is, deterioration from baseline status of 0 or 1).

Time to deterioration in FHSI-8 is defined as the time from the date of randomization to the first date observing a decrease ≥3 points from baseline. Survival curves and median with 95% CI will be estimated using the Kaplan-Meier methodology and will be compared using a Cox regression model and log-rank test.

Safety: Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Adverse events and clinical laboratory values will be graded using the Common Terminology Criteria for Adverse Events Version 4.0. Adverse events, drug exposure, hospitalizations due to adverse events, vital signs, and transfusions will be summarized.

Health Outcomes: Patient-reported outcomes, including disease-specific symptoms and health status, will be assessed using the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8) and the EuroQol 5-Dimension 5 Level (EQ-5D-5L).

Immunogenicity: Blood samples will be collected at specified time points, and in the event of an infusion-related reaction, to determine antibody production against ramucirumab or placebo.

Pharmacokinetics: Blood samples will be collected at specified time points, and in the event of an infusion-related reaction, for assessment of ramucirumab serum concentrations.

Exploratory Biomarker Research: Tumor tissue, plasma, and whole blood will be collected and assayed for biomarkers relevant to ramucirumab, angiogenesis, and the disease state, and to correlate these markers to clinical outcome.

Statistical Methods:

Statistical: The primary objective of this study is to compare ramucirumab versus placebo in terms of OS in patients with advanced HCC after intolerance or progression on prior sorafenib. The sample size of approximately 279 patients was determined based on the following assumptions:

- a hazard ratio (HR) of 0.67, with median OS of 4.5 months in the placebo arm and 6.7 months in the ramucirumab arm
- 2:1 randomization (ramucirumab:placebo)
- the overall significance level will be controlled at 1-sided 0.025 (2-sided 0.05)
- the Type II error rate is 20%, that is, 80% statistical power

Under the assumptions above, the final analysis will be performed after approximately 221 deaths have been observed (assuming 20% censoring rate including dropouts).

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

A gatekeeping approach for selected secondary endpoints will be applied in order to protect the study-wise type I error rate and enable inferential statements; each hypothesis will be inferentially tested only if each of the preceding hypotheses were rejected. The sequential order of the confirmatory testing in the intent-to-treat (ITT) population will be: OS, progression-free survival (PFS), time to deterioration in FHSI-8, and time to deterioration in ECOG PS.

Interim analyses will be prepared by an independent statistical analysis center. An independent data monitoring committee will monitor the overall study conduct and perform reviews of safety data.

Efficacy: The analysis of OS will be based on a stratified log-rank test, stratified by randomization strata as recorded in the Interactive Web Response System (IWRS). OS curves, median OS with 95% confidence interval (CI), and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method. The HR will be estimated using a stratified Cox regression model, stratified by randomization strata as recorded in the IWRS. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint. Sensitivity analyses of OS will include: unstratified log-rank test and Cox models; analysis for the per-protocol population; and univariate and multivariate Cox regression model to explore potential prognostic and/or predictive factors. Additional sensitivity analyses may be specified in the SAP.

Analysis of PFS will be based on stratified log-rank test, stratified by randomization strata as recorded in the IWRS. PFS survival curves, median PFS with 95% CI, and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method. The HR will be estimated using a stratified Cox regression model, stratified by randomization strata as recorded in the IWRS. Sensitivity analyses will be performed for PFS: unstratified log-rank test and Cox models; analysis for the per-protocol population; analysis including both radiographic and clinical progressions as PFS events; sensitivity analysis for various PFS censoring rules (for example, postdiscontinuation systemic anticancer therapy, missing 2 or more tumor assessments prior to PD/death); and univariate and multivariate Cox regression models will be used to explore potential prognostic and/or predictive factors. Additional sensitivity analyses may be specified in the SAP.

Best overall response will be determined using RECIST Version 1.1. ORR will be calculated as the number of patients who achieve a best overall response of complete response (CR) or partial response (PR), divided by the total number of patients randomized to the corresponding treatment group (ITT population). The disease control rate (DCR) will be calculated as the number of patients who achieve a best overall response of CR, PR, or stable disease, divided by the total number of patients randomized to the corresponding treatment group (ITT population). Patients who do not have a tumor response assessment for any reason will be considered as nonresponders and will be included in the denominator of the response rate calculation. The ORR or DCR with 95% CI observed in each treatment group will be summarized and compared using the Cochran-Mantel-Haenszel test adjusting for the randomization strata.

Time to progression will be compared between treatment groups (ITT population) using the stratified log-rank test and the stratified Cox regression model; survival curves will be estimated using the Kaplan-Meier methodology. Additional sensitivity analyses using alternative censoring rules may be performed.

Time to deterioration in ECOG PS will be compared between treatment groups. Survival curves and median with 95% CI will be estimated using the Kaplan-Meier methodology and will be compared using a Cox regression model and log-rank test.

Safety: Safety analyses will be based on the safety population (all randomized patients who receive any quantity of ramucirumab or placebo, regardless of their eligibility for the study). Evaluations will be performed based on the actual study treatment received, regardless of the patient's assigned treatment arm.

Adverse events (AEs) will be summarized (incidence and percentage of patients) overall, by causality (relationship to study drug), action taken, and outcome. Duration of AEs will be determined and included in the listings. Study drug exposure will be summarized for each treatment arm with the following variables: number of infusion, number of cycles, duration of therapy, cumulative dose, dose intensity, and relative dose intensity. Incidence of laboratory abnormalities, hospitalizations due to AEs, transfusions, and vital signs will be summarized.

Health Outcomes: FHSI-8 scores and their change from baseline will be summarized descriptively at each assessment time point. The change from baseline in FHSI-8 will be compared to determine whether statistically significant differences exist between the ramucirumab and placebo arms. The visual analogue scale will be scored from 0 (worst imaginable health state) through 100 (best imaginable health state). Summary statistics will be provided.
Pharmacokinetics and Immunogenicity: Serum concentrations of study drug (ramucirumab or placebo) prior to infusion (trough concentration) and at 1 hour after the end of the infusion (approximately peak concentration) will be summarized using descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate. Relationships between ramucirumab exposure and measures of efficacy and safety will be explored. Immunogenicity incidence will be tabulated, and correlation of immunogenicity to ramucirumab drug level, activity, and safety will be assessed as appropriate. Exploratory Biomarker Research: Assay results will be summarized and correlated with clinical outcomes.

3. Table of Contents

Randomized, Double-Blind, Placebo Controlled, Phase 3 Study of Ramucirumab and Best Supportive Care (BSC) Versus Placebo and BSC as Second-Line Treatment in Patients With Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-Line Therapy With Sorafenib

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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.
AESI	adverse event of special interest
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
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
ATE	arterial thromboembolic event
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BCLC	Barcelona Clinic Liver Cancer
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment. Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and study site staff are aware of the treatment but the patient is not, or vice versa, or when Lilly is aware of the treatment but the investigator, study site personnel, and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or Lilly staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BP	blood pressure
BSC	best supportive care
CHF	congestive heart failure
CI	confidence interval
collection database	A computer database where clinical trial data are entered and validated.

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.
continued access period	The period between study completion and end of trial during which patients on ramucirumab who continue to experience clinical benefit and no undue risks may continue to receive ramucirumab until one of the criteria for discontinuation is met.
CR	complete response
CrCl	creatinine clearance
CRF	case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FACT	Functional Assessment of Cancer Therapy

FHSI-8	FACT Hepatobiliary Symptom Index-8
GCP	good clinical practice
GI	gastrointestinal
HCC	hepatocellular carcinoma
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
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.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product (IP) includes a product with a marketing authorization when: • used or assembled (formulated or packaged) in a way different from the authorized form, • used for an unauthorized indication, or • 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.
IRB	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.
IRR	infusion-related reaction

ITT	intention-to-treat The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
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
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	Preferred Term
PTT	partial thromboplastin time
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	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, 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
Study completion	This study will be considered complete after the final analysis of overall survival is performed.
SUSARs	suspected unexpected serious adverse reactions
[redacted]	[redacted]
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TTP	time to progression
ULN	upper limits of normal
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event

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5. Introduction

Hepatocellular carcinoma (HCC) is a highly vascular neoplasm characterized by arterial enhancement relative to non-neoplastic liver on computed tomography (CT) and magnetic resonance imaging (MRI) (Honda et al. 1999; Gogel et al. 2000). Circulating vascular endothelial growth factor (VEGF) levels are increased in HCC (Jinno et al. 1998; Poon et al. 2001; Kim et al. 2004) and have been shown to correlate with tumor VEGF expression (Poon et al. 2003). High tumor microvessel density and increased local and circulating VEGF are associated with rapid disease progression and reduced survival (Chow et al. 1997; Miura et al. 1997; El-Assal et al. 1998; Li et al. 1998; Torimura et al. 1998; Shimoda et al. 1999).

The global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study I4T-IE-JVBF (REACH) evaluated the efficacy and safety of ramucirumab as a single agent for the treatment of patients with advanced HCC after prior sorafenib therapy. REACH demonstrated a numerical improvement in the primary endpoint of overall survival (OS), though this benefit was not statistically significant. A robust improvement in the secondary endpoints of progression-free survival (PFS), time to progression (TTP), and objective response rate (ORR) was observed in the ramucirumab arm compared with the placebo arm. The efficacy results are supported by sensitivity analyses and subgroup analyses. Taken together, the efficacy results from REACH support the hypothesis that ramucirumab treatment may provide meaningful benefits for patients with HCC.

In preplanned and exploratory analyses of REACH, ramucirumab treatment led to a progressively greater reduction in the risk of death (that is, a more favorable hazard ratio [HR]) in patients with progressively higher baseline alpha-fetoprotein (AFP) values. In the population with a baseline AFP ≥400 ng/mL, as assessed by local clinical laboratories, a robust and clinically meaningful improvement in OS was observed (HR 0.674; median OS 7.8 months for ramucirumab vs. 4.2 months for placebo; p=0.0059).

The REACH results show that ramucirumab has activity and a manageable safety profile in HCC patients with elevated baseline AFP. Given the number of agents that have failed in HCC clinical trials, selection of patients will likely be required for any new agents to demonstrate a survival benefit. For ramucirumab, patients with a baseline AFP ≥400 ng/mL derived survival benefit in REACH, and the survival benefit from ramucirumab treatment in this selected patient population with a baseline AFP ≥400 ng/mL will be assessed in this trial JVDE.

More information about the known and expected benefits, risks and reasonably anticipated adverse events (AEs) of ramucirumab may be found in the Investigator's Brochure (IB) and the local label. Information on AEs expected to be related to ramucirumab may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure that will be assessed by Lilly in aggregate periodically during the course of the study may be found in Section 6 (Effects in Humans) of the IB.

6. Objectives

6.1. Primary Objective

The primary objective is to compare overall survival (OS) for ramucirumab versus placebo in patients with advanced HCC after intolerance or progression on prior sorafenib treatment.

6.2. Secondary Objectives

The secondary objectives of the study are to evaluate:

- Progression-free survival (PFS)
- Time to radiographic progression (TTP)
- Objective response rate (ORR)
- Safety profile of ramucirumab
- Ramucirumab pharmacokinetics (PK)
- Immunogenicity of ramucirumab
- Time to deterioration in Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8)
- Time to deterioration in Eastern Cooperative Oncology Group performance status (ECOG PS)
- Other patient-reported outcome (PRO) measures of disease-specific symptoms and health-related quality of life

6.3. Exploratory Objectives

The exploratory objective of the study is to investigate biomarkers relevant to ramucirumab, angiogenesis, and the disease state and to correlate these markers to clinical outcome.

7. Study Population

Individuals who do not meet the criteria for participation in this study (screen failures) may be re-screened, only after discussion with and permission from the Lilly clinical research physician (CRP)/clinical research scientist or designee. Each time re-screening is performed, an individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

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] The patient has a diagnosis of HCC based on either:

a. histopathologic or cytologic findings

b. in the absence of histologic confirmation, a diagnosis of cirrhosis and HCC with classical imaging characteristics (that is, at least a 3-phase liver protocol CT or MRI and a lesion that demonstrates arterial hyperenhancement and washes out in the venous phase).

[2] The patient received sorafenib treatment for at least 14 days and discontinued sorafenib treatment ≥14 days prior to randomization.

[3] The patient experienced radiographically confirmed disease progression during or after discontinuation of sorafenib therapy or discontinued sorafenib treatment because of intolerance despite appropriate sorafenib management and supportive care.

[4] The patient received sorafenib as the only systemic therapeutic intervention for advanced HCC.

[5] The patient has ≥1 measurable lesion per Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 (Eisenhauer et al. 2009) that has not been previously treated with locoregional therapy. A patient with a lesion(s) that has previously been treated with locoregional therapy is also eligible, if the lesion has documented progression after locoregional treatment and is measureable.

[6] The patient is ≥18 years of age or of an age acceptable according to local regulations, whichever is older.

[7] The patient has a Child-Pugh score of <7 (Child-Pugh Class A only) (Child and Turcotte 1964; Pugh et al. 1973; Lucey et al. 1997).

[8] The patient has Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy.

[9] The patient has a baseline AFP ≥400 ng/mL, as determined by local laboratory testing. See Section 10.4.1 for AFP testing requirements.

[10] The patient has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

[11] The patient has resolution of all clinically significant toxic effects of prior locoregional therapy, surgery, or other anticancer therapy to Grade ≤1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE; Version 4.0]).

[12] The patient has adequate organ function as determined by:

a. Hepatic: Total bilirubin ≤1.5 times upper limit of institutional normal value (ULN), aspartate transaminase (AST) and alanine transaminase (ALT) ≤5 × ULN.

b. Renal:

i. Calculated creatinine clearance is ≥60 mL/min as per the Cockcroft-Gault formula (Attachment 6) or equivalent method (such as 24-hour urine collection). Methods using radiolabeled markers (such as 51-CrEDTA or Tc99m-DTPA) to determine glomerular filtration rate are also acceptable.

ii. The patient's urinary protein is ≤1+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine must be collected and must demonstrate <1 g of protein in 24 hours to allow participation in the study.

c. Hematologic: Absolute neutrophil count ≥1.0 × 10^9/L, hemoglobin ≥9 g/dL (5.58 mmol/L), and platelets ≥75 × 10^9/L; blood-product transfusions are not allowed within 1 week prior to baseline laboratory evaluations. Recent (<2 months prior to randomization) use of growth factor support is not allowed.

d. Coagulation: The patient must have adequate coagulation function as defined by International Normalized Ratio (INR) ≤1.5 and a partial thromboplastin time (PTT) ≤5 seconds above the ULN. Patients receiving low-dose anticoagulant therapy at prophylactic doses are eligible provided that INR ≤1.5 and PTT ≤5 seconds above the ULN.

[13] The patient meets the more stringent of the following requirements:

a. local requirements regarding methods and duration of contraception.

b. if female, the patient is surgically sterile, postmenopausal, or compliant with a highly effective contraceptive method (failure rate <1%) during and for 12 weeks after the study treatment period. Oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method.

if male, the patient is surgically sterile or compliant with a highly effective contraceptive method (failure rate <1%) during and for 12 weeks after the study treatment period.

[14] The patient, if a woman of childbearing potential, has a negative serum pregnancy test within 7 days prior to randomization.

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

[16] The patient is willing to provide blood/serum for research purposes. Submission of blood/serum is mandatory for participation in this study, unless restricted per local regulations.

7.2. Exclusion Criteria

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

[17] The patient has or had fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma.

[18] The patient had a previous or has concurrent malignancy. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low, as judged by the investigator, may be eligible for this study in consultation with and approval by the Lilly CRP.

[19] The patient has previously documented brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression.

[20] The patient has a history of or current hepatic encephalopathy (any grade) or clinically meaningful ascites. Clinically meaningful ascites is defined as CTCAE Grade >1 ascites resulting from cirrhosis. Patients who have been on a stable medical regimen (for ≥3 months) to manage ascites are eligible if they show no evidence of ascites on clinical exam that would require further intervention.

[21] The patient has ongoing or recent (≤6 months prior to randomization) hepatorenal syndrome.

[22] The patient had a prior liver transplant.

[23] The patient received any previous systemic therapy with VEGF inhibitors or VEGF-Receptor inhibitors (including investigational agents) other than sorafenib for treatment of HCC.

[24] The patient received any hepatic locoregional therapy (including radiation, surgery, hepatic arterial embolization, chemoembolization, radiofrequency ablation, cryoablation, or percutaneous ethanol injection) following sorafenib or within 28 days prior to randomization. Use of locoregional therapy *prior* to sorafenib is allowed.

[25] The patient received radiation to any nonhepatic (for example, bone) site within 14 days prior to randomization. Prior radiation to >25% total bone marrow is not allowed.

[26] The patient experienced either of the following:

a. a major surgical procedure, significant traumatic injury, non-healing wound, peptic ulcer, or bone fracture ≤28 days prior to randomization, or

b. placement of a subcutaneous venous access device within 7 days prior to the first dose of study treatment unless the procedure is of low risk for bleeding in the judgment of the investigator (for example, introduction of peripherally inserted central catheter line).

Study medications can be commenced only after complete wound healing.

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

[28] The patient discontinued from study treatment from another clinical trial within 28 days prior to randomization.

[29] The patient has a known allergy or hypersensitivity reaction to any of the treatment components.

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

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

[31] The patient experienced any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to randomization.

[32] The patient experienced any bleeding episode considered life-threatening, or any Grade 3 or 4 gastrointestinal/variceal bleeding episode in the 3 months prior to randomization requiring transfusion or endoscopic or operative intervention.

[33] The patient has esophageal or gastric varices that require immediate intervention (for example, banding or sclerotherapy) or represent a high bleeding risk in the opinion of the investigator or consulting gastroenterologist or hepatologist. Patients with evidence of portal hypertension (including splenomegaly detected radiographically) or any prior history of variceal bleeding must have had endoscopic evaluation within the 3 months immediately prior to randomization.

[34] The patient has a history of gastrointestinal perforation and/or fistulae within 6 months prior to randomization.

[35] The patient has symptomatic congestive heart failure (New York Heart Association II-IV), unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia.

[36] The patient is pregnant or breast-feeding.

[37] The patient has an 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. Such conditions or abnormalities include but are not limited to:

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

b. Active or uncontrolled clinically serious infection. (Patients with chronic viral hepatitis are eligible.)

c. Ongoing or recent history of drug abuse.

d. The patient has a history of uncontrolled hereditary or acquired thrombotic or bleeding disorder.

[38] The patient has 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.

[39] The patient is receiving therapeutic dose anticoagulation with warfarin, low-molecular-weight heparin, or similar agents.

[40] The patient is receiving chronic therapy with nonsteroidal anti-inflammatory agents (such as indomethacin, ibuprofen, naproxen or similar agents) or other anti-platelet agents (such as clopidogrel, ticlopidine, dipyridamole, or anagrelide). Aspirin at doses up to 100 mg/day is permitted.

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

7.3. Discontinuation

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

Patients who are discontinued from study treatment early will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

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

7.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigative site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, Lilly must be notified. If Lilly identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigative site will be notified. A discussion must occur between the Lilly CRP and the investigator to determine whether it is medically appropriate for the patient to continue in the study, with or without study treatment. The investigator must obtain documented approval from the Lilly CRP to allow an inadvertently enrolled patient to continue in the study, with or without study treatment.

7.3.2. Discontinuation of Study Treatment

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

- The patient is enrolled in any other clinical trial involving an investigational product or in any other type of medical research judged not to be scientifically or medically compatible with this study.
- The patient, for any reason, requires treatment with another therapeutic agent that has demonstrated effectiveness for treatment of the study indication, discontinuation from study treatment will occur prior to introduction of the new agent.
- The patient requests to be withdrawn from study treatment.
- The patient is significantly noncompliant with study procedures and/or treatment.
- The investigator decides that the patient should be discontinued from study treatment.
- Unacceptable toxicity. Refer to Table JVDE.3 and to Table JVDE.4 for information about discontinuation from study treatment due to AEs.
- Any study treatment-related event that is deemed life-threatening, regardless of NCI-CTCAE grade, if the event is considered possibly related to study treatment.
- The patient requires any of the following:
  1. >2 dose reductions
  2. ≥2 consecutive missed doses of study treatment
  3. a dose delay of >21 days

In the case of 2 or 3 above, continuation of study treatment may be considered, however, subject to the requirements stated in Section 9.4.2.

- A deterioration in ECOG PS to 3 or worse during the course of therapy on study despite optimal supportive care, even in the absence of radiographic evidence of disease progression.
- Disease progression (assessed radiologically or clinically). If the patient is experiencing a treatment benefit in the opinion of the investigator, the patient may continue study treatment beyond radiographic progression until clinical progression. Determination of clinical progression is at the discretion of the investigator and may include both objective and subjective data.

If treatment is discontinued for any reason other than radiographically confirmed progressive disease (PD) or withdrawal of consent, radiographic tumor assessments will continue according to the protocol schedule, except when not feasible, in the opinion of the investigator, because of the patient's clinical status.

7.3.3. Discontinuation from the Study

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

- The investigator decides that the patient should be discontinued from the study.
- The patient requests to be withdrawn from the study.
- The patient becomes pregnant during the study.
- Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

7.3.4. Patients Who Are Lost to Follow-Up

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

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

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

7.3.5. Discontinuation of Study Sites

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

7.3.6. Discontinuation of the Study

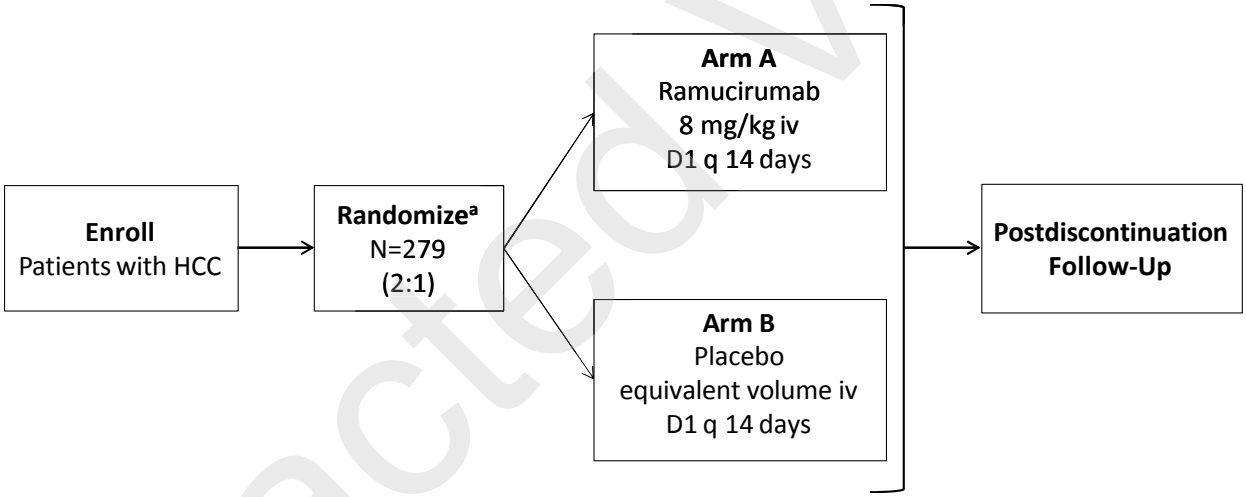
The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

Study JVDE is a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study evaluating the efficacy and safety of ramucirumab as a single agent for the treatment of patients with advanced HCC and elevated baseline AFP after intolerance or progression on prior sorafenib therapy. The primary objective is to compare the overall survival of HCC patients treated with ramucirumab versus patients treated with placebo. Patients with a baseline AFP ≥400 ng/mL, based on local laboratory results, who meet all other inclusion/ exclusion criteria, will be enrolled. The study will randomize (in a 2:1 ratio) approximately 279 patients with a baseline AFP ≥400 ng/mL to receive ramucirumab 8 mg/kg or placebo administered intravenously once every 14 days in an outpatient setting. All patients will be offered best supportive care (BSC), as determined appropriate by the investigator. Study treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or until other withdrawal criterion is met.

Figure JVDE.1 illustrates the study design.



Abbreviations: D = Day; ECOG PS = Eastern Cooperative Oncology Group performance status; HCC = hepatocellular carcinoma; iv = intravenous; N = number of randomized patients; q = every; vs = versus.

[a] Stratified by region (Region 1 vs Region 2 vs Region 3), macrovascular invasion (yes vs no), and ECOG PS (0 vs 1). Region 1 includes the Americas, Europe, Israel, and Australia; Region 2 includes Asian countries (excluding Japan); and Region 3 includes Japan only.

Figure JVDE.1. Illustration of study design.

The following terms describe the stages through which the patients will progress during the course of the study, as shown in Figure JVDE.2. Refer to the study schedule (Attachment 1) for the timing of procedures to be performed at each stage of the study.

- **Baseline:** begins when the ICF is signed and ends at the first study treatment (or at discontinuation, if no treatment is given). All assessments required for eligibility must be performed prior to randomization.
- **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. The date of this agreement is to be reported on the case report form (CRF) as the *Date of Discontinuation* from study treatment.
- **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.

  Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days) (until the short-term 30-day safety follow-up visit is completed). Patients who are in short-term follow-up when the continued access period begins (Section 8.1.1.2) will continue in short-term follow-up until short-term follow-up is completed. Assessments scheduled on Days 1 to 7 of the short-term follow-up period (see Attachment 1) may also be performed on the same day the patient and the investigator agree that the patient will no longer continue study treatment.

  Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or study completion, whichever occurs first. Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

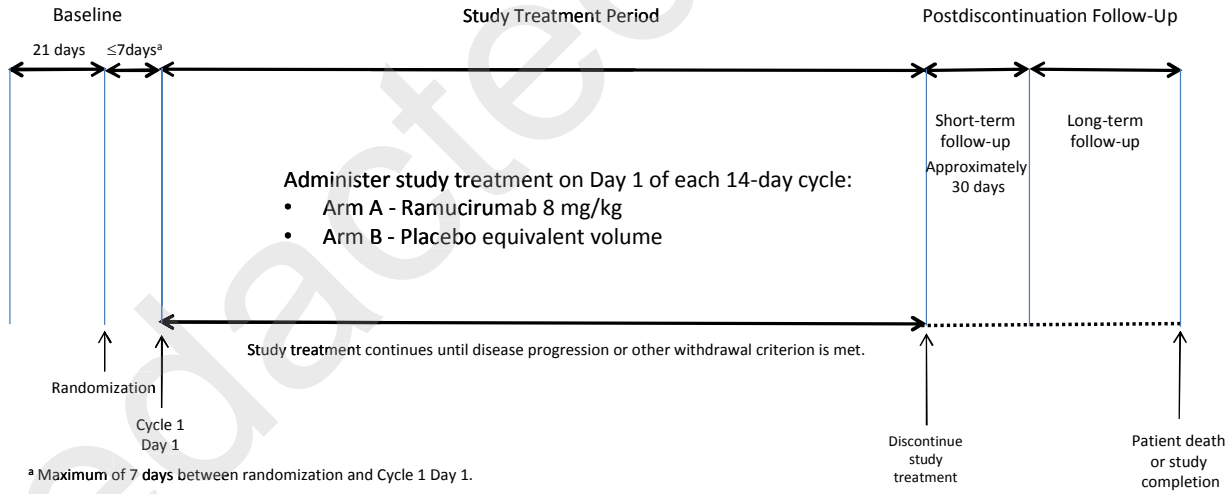


Figure JVDE.2. Patient flow diagram.

8.1.1. Study Completion, Continued Access, and End of Trial

8.1.1.1. Study Completion

Study completion will occur when survival data have been fully analyzed. Lilly will notify investigators when study completion occurs (Figure JVDE.3). All patients who are still on study

treatment when study completion occurs will be unblinded. If ≥1 patient is still on ramucirumab when study completion occurs, Lilly will notify investigators when the continued access period will begin.

8.1.1.2. Continued Access

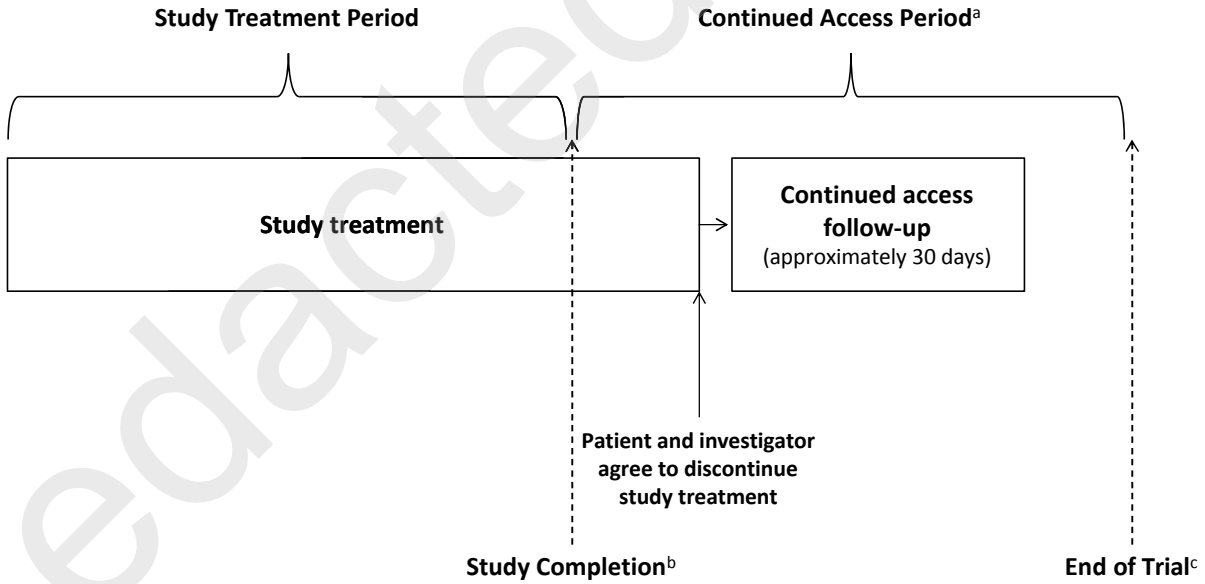
Patients who are still on ramucirumab at study completion may continue to receive ramucirumab if they are experiencing clinical benefit and no undue risks are identified. Continued access to ramucirumab will end when a criterion for discontinuation is met (Section 7.3). Continued access follow-up will begin the day after the patient and the investigator agree to discontinue ramucirumab and will last approximately 30 (±7) days. Placebo is not to be administered during the continued access period.

Patients on the placebo arm may be permitted to crossover to the ramucirumab arm at study completion and enter the continued access period of the study. Crossover may be permitted at study completion, if, in the opinion of the investigator and sponsor, the patient would benefit from receiving ramucirumab.

The study schedule for the continued access period is shown in Attachment 2.

8.1.1.3. End of Trial

The term "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 continued access follow-up.



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Lilly will notify sites when study completion occurs.
[c] End of trial occurs at the last visit or last scheduled procedure for the last patient.

Figure JVDE.3. Study completion, continued access, and end of trial.

8.2. Discussion of Design and Control

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study treatment and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study treatment and minimizes bias in the assessment and interpretation of observed treatment effects.

To further reduce the potential for bias and improve the power of the analyses, patients will be stratified for differences in factors thought to be associated with clinical outcomes. Assessment of bias is further minimized by the use of a double blind and placebo control.

Currently, no agent has improved survival of patients with advanced HCC over BSC following progression on and/or intolerance to sorafenib. Given the lack of a regimen specifically approved in this setting, or an established standard of care, single-agent ramucirumab (plus BSC) was selected for the investigational arm to allow demonstration of potential benefit with ramucirumab. Placebo plus BSC is considered an appropriate control in this setting consistent with current guidelines on HCC (Llovet et al. 2008a; Thomas et al. 2010; EASL-EORTC 2012).

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in this study:

- Arm A: ramucirumab 8 mg/kg
- Arm B: placebo (equivalent volume)

Study treatment (ramucirumab or placebo) will be administered as an intravenous infusion once per 14-day cycle. See Section 9.4 for more information about the timing of study treatment. All patients will receive BSC.

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

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

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

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

9.2. Materials and Supplies

Ramucirumab and placebo will be provided by Lilly and will be labeled according to the country's regulatory requirements.

9.2.1. Ramucirumab

[redacted]

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

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

9.2.2. Placebo

[redacted]

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

9.3. Method of Assignment to Treatment

After the patient signs the ICF, the site will register the patient via the Interactive Web Response System (IWRS), which is accessible 24 hours a day. IWRS registration consists of assigning the patient a unique study identification number, after which screening for eligibility may commence. Upon completion of all screening evaluations to confirm a patient's eligibility, sites will utilize IWRS to randomize the patient to 1 of the 2 treatment arms. Once the patient is randomized through the IWRS, he/she is considered to be enrolled in the study.

Randomization will be stratified by the following factors:

1. geographic region (Region 1 versus Region 2 versus Region 3)
2. macrovascular invasion (yes versus no)
3. ECOG performance status (0 versus 1)

The general plan for assigning participating countries to a geographic region is as follows:

1. Region 1 will include the Americas, Europe, Israel, and Australia.
2. Region 2 will include countries in Asia (excluding Japan).
3. Region 3 will include Japan only.

Participating countries not specifically described above will be assigned to Region 1, 2, or 3, as deemed appropriate by the study team. Specific details about the countries assigned to each region will be provided in the statistical analysis plan (SAP).

9.4. Selection and Timing of Doses

A cycle is defined as an interval of 14 days. In Cycle 1, study treatment should be administered within 7 days after the patient's randomization date. If the Cycle 1 infusion cannot be administered within 7 days after the patient's randomization date, study treatment must be delayed until laboratory tests are repeated and the case is discussed with the Lilly CRP. See *Laboratory Evaluations* in the study schedule (Attachment 1).

In subsequent cycles, study treatment may be administered up to 3 days before or up to 3 days after the patient's scheduled dose.

The actual doses of ramucirumab and placebo to be administered will be determined by measuring the patient's weight in kilograms at the beginning of each cycle. If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, the dose will not need to be recalculated. A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

A patient may continue to receive study treatment until a criterion for discontinuation is met (as described in Section 7.3).

9.4.1. Preparation and Administration of Study Treatment

9.4.1.1. Preparation

Aseptic technique is to be used when preparing and handling study treatment for infusion.

Ramucirumab and placebo are compatible with common infusion containers. The use of a low protein binding 0.22-micron in-line filter is required. Details regarding infusion sets that are compatible for ramucirumab infusion can be found in the study pharmacy manual and the IB.

Based on the calculated volume of ramucirumab/placebo, add (or remove from pre-filled with 0.9% normal saline intravenous 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. Further details regarding study drug preparation can be found in the study pharmacy manual and the IB.

9.4.1.2. Premedication

Premedication with a histamine H_1 antagonist, such as diphenhydramine hydrochloride (or equivalent), is required prior to infusion of ramucirumab/placebo. Additional premedication may be provided at the discretion of the investigator. See Table JVDE.3 for dose modifications and additional premedication requirements for patients who have experienced a prior infusion-related reaction (IRR). All premedication administered must be adequately documented on the CRF.

9.4.1.3. Administration of Study Treatment

Treatment should commence only if all the inclusion and exclusion criteria are met, and the patient has been randomized to Arm A (ramucirumab) or Arm B (placebo) via IWRS. For subsequent cycles, dose modifications are permitted as described in Section 9.4.2. All study treatment will be discontinued in the event of disease progression (Section 7.3.2).

Prior to each infusion of study treatment, the patient must meet the criteria shown in Table JVDE.1.

Table JVDE.1. Criteria to Be Met Prior to Each Infusion of Study Treatment

Event	Requirement
AESI	Refer to Table JVDE.3
Other clinically significant toxicity or AE related to study treatment, as determined by the investigator	The event must be resolved to CTCAE (Version 4.0) Grade <2 or the patient's baseline level

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CTCAE = Common Toxicity Criteria for Adverse Events (NCI 2009).

Ramucirumab or placebo should be delivered via infusion pump in approximately 60 minutes. The infusion rate should not exceed 25 mg per minute. Infusions >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 IRR); the infusion duration must always be accurately recorded. After the infusion, the infusion set must be flushed with sterile 0.9% normal saline greater than or equal to infusion set hold-up volume to ensure delivery of the calculated dose.

CAUTION: Infusion-related reactions (IRRs) may occur during or following administration of study treatment. During the infusion, patients should be in an area that has available resuscitation equipment and treatments necessary for advanced life support and cardiopulmonary resuscitation (CPR), such as bronchodilators, vasopressor agents (for example, epinephrine), oxygen, glucocorticoids, antihistamines, intravenous fluids, and so forth. A 1-hour observation period is required after the administration of the first 2 doses of ramucirumab. If no evidence of an IRR is observed during the initial 2 cycles of study treatment, then no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, then the 1-hour observation should be reinstituted.

9.4.2. Dose Modifications

Dose modifications are permitted for non-life-threatening Grade 3 clinical AEs (such as fever) that are considered to be at least possibly related to study treatment and that resolve to Grade ≤1 or to the patient's pretreatment baseline level within 1 treatment cycle (approximately 2 weeks). Discontinue study treatment if the patient experiences a Grade 4 AE, other than Grade 4 fever or Grade 4 laboratory abnormalities, that is at least possibly related to study treatment.

Table JVDE.3 presents the criteria for dose modifications that are applicable if a patient experiences an adverse event that is considered an *adverse event of special interest* (AESI). A list of the AESIs is provided below. Detailed information about AESIs is provided in Section 10.3.1.1.

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

Table JVDE.4 presents the criteria for dose modifications that apply if a patient experiences an AE that is not an AESI.

Any patient who requires a dose reduction will continue to receive a reduced dose until discontinuation from study treatment, or discontinuation from the study. No dose escalations are allowed after a dose reduction. Any patient who has had 2 dose reductions and who experiences a toxicity that would cause a third dose reduction, must be discontinued from study treatment.

Table JVDE.2 presents the specific dose reductions applicable to both treatment arms.

Table JVDE.2. Dose Reductions[a]

	Dose
Starting dose	8 mg/kg
First dose reduction	6 mg/kg
Second dose reduction	5 mg/kg

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

If a patient is unable to receive study treatment on the date of his/her regularly scheduled dose (±3 days) for any reason (including AEs), the next dose of study treatment should be administered at the next regularly scheduled treatment time point following the resolution of the event that caused the delay (treatment in this situation is considered to occur at the numbered cycle immediately following the last cycle in which the patient received study treatment). Make-up doses occurring between regularly scheduled (every-14-days) treatment time points are not permitted.

Study treatment may be delayed for up to 21 days to allow time for a patient to recover from an AE or laboratory toxicity. If a patient misses ≥2 consecutive doses or requires a dose delay of >21 days, continuation of study treatment may be considered after consultation with the Lilly CRP, if both of the following criteria are met:

- the events related to the missed/delayed doses have been resolved
- the patient shows evidence of ongoing disease control

Table JVDE.3. Dose-Modification Guidelines for Adverse Events of Special Interest

Adverse Event of Special Interest		Dose Modification
1.	**Infusion-related reaction** (Section 10.3.1.1.1)	
1.a.	• Infusion-related reaction - Grade 1 or 2	Reduce the infusion rate by 50% for the duration of the infusion and for all future infusions. Prior to all future infusions, premedicate with: • a histamine H1 antagonist, such as diphenhydramine hydrochloride • dexamethasone or equivalent • acetaminophen
1.b.	• Infusion-related reaction - Grade 3 or 4	Discontinue study treatment.
2.	**Hypertension** (Section 10.3.1.1.2)	
2.a.	• Hypertension (non-life-threatening) - Grade 2 or 3	Delay ramucirumab until the hypertension is controlled with medication and is resolved to Grade <2. • If controlled with medication and resolved to Grade <2, then resume study treatment at current dose. • If **not** controlled with medication and **not** resolved to Grade <2 within **21 days**, then discontinue study treatment. • For patients with asymptomatic Grade 2 hypertension, investigators have the discretion to consider the clinical circumstances of individual patients and administer unchanged dose of study treatment.
2.b.	• Uncontrolled hypertension, hypertensive crisis, or hypertensive encephalopathy - Grade 4	Discontinue study treatment.
3.	**Proteinuria** (Section 10.3.1.1.3)	
3.a.	• Proteinuria =2+ (dipstick or routine urinalysis)[a]	• Administer study treatment at the patient's current dose if clinically indicated. • Obtain 24-hour urine protein results within 3 days prior to the next infusion. o If urine protein is <2 g/24 h, administer study treatment at the patient's current dose. o If urine protein is ≥2 g/24 h, modify the dose based on 24-hour collection. See *Proteinuria ≥2 g/24 h (24-hour urine collection)*, Line 3.c in this table.
3.b.	• Proteinuria >2+ (dipstick or routine urinalysis)[a]	• Delay study treatment for up to 21 days. • Obtain 24-hour urine protein results within 3 days prior to the next infusion. o If urine protein is <2 g/24 h, no further dose delay or dose reduction is required. o If urine protein is ≥2 g/24 h, modify the dose based on 24-hour collection. See *Proteinuria ≥2 g/24 h (24-hour urine collection)*, Line 3.c in this table.

Adverse Event of Special Interest		Dose Modification
3.c.	• Proteinuria ≥2 g/24 h (24-hour urine collection)[a]	**First or second occurrence**: delay study treatment until urine protein returns to <2 g/24 h. Reduce the dose as shown in Table JVDE.2. If urine protein remains ≥2 g/24 h after 21 days, discontinue study treatment. **Third occurrence**: discontinue study treatment.
3.d.	• Proteinuria >3 g/24 h **or** in the setting of nephrotic syndrome[a]	Discontinue study treatment.
4.	Arterial thromboembolic events, venous thromboembolic events (Section 10.3.1.1.4) - Grade 3 or 4	Discontinue study treatment.
5.	Bleeding (Section 10.3.1.1.5) - Grade 3 or 4	Discontinue study treatment.
6.	Gastrointestinal perforation (Section 10.3.1.1.6)	Discontinue study treatment.
7.	Reversible posterior leukoencephalopathy syndrome (Section 10.3.1.1.7)	Discontinue study treatment.
8.	Congestive heart failure (Section 10.3.1.1.8) – Grade 3 or 4	Discontinue study treatment.
9.	Fistula formation (Section 10.3.1.1.9)	Discontinue study treatment.
10.	Impaired wound healing (Section 10.3.1.1.10)	
10.a.	• Prior to planned surgery	Withhold study treatment.
10.b	• After surgery	Resume study treatment based on clinical judgment (maximum delay is 21 days).
10.c.	• Wound-healing complications developed during study treatment	Delay study treatment dosing (for up to 21 days) until the wound is fully healed.
11.	Liver injury/liver failure (Section 10.3.1.1.11)	
11.a.	• Hepatic encephalopathy and/or hepatorenal syndrome	Discontinue study treatment.

[a] Perform dipstick or routine urinalysis within 72 hours prior to each infusion of ramucirumab (see Table JVDE.1). If 24-hour urine collection is also performed, the results of 24-hour urine collection should be used for clinical decision-making.

Table JVDE.4. Dose Modifications for Adverse Events That Are Not Adverse Events of Special Interest

AE or Toxicity	Dose Modification	
Grade 2 clinical AE or Grade 2 laboratory abnormality that is (a) reversible and (b) not life-threatening **Grade 3 laboratory abnormality** that is: (a) not clinically significant and (b) unrelated to study treatment	At the discretion of the investigator, study treatment may be delayed for up to 21 days. Dose reduction is not required.	
Grade 3 or 4 clinical AE that is unrelated to study treatment **Grade 4 laboratory abnormality** that is: (a) clinically insignificant and (b) unrelated to study treatment	At the discretion of the investigator, study treatment may be delayed for up to 21 days. If the investigator chooses to delay study treatment, follow the instructions below:	
	If the event resolves to Grade <2 or the patient's baseline level within 21 days	**Then**, resume study treatment, at the discretion of the investigator. Dose reduction is not required.
	If the event does not resolve to Grade <2 or the patient's baseline level within 21 days	**Then**, discontinue study treatment.
Grade 3 clinical AE that is at least possibly related to study treatment	Delay study treatment for up to 21 days.	
	If the event resolves to Grade <2 or the patient's baseline level within 21 days	**Then**, resume study treatment at a reduced dose, as shown in Table JVDE.2.
	If the event does not resolve Grade <2 or the patient's baseline level within 21 days	**Then**, discontinue study treatment.
Grade 3 or 4 fever that is at least possibly related to study treatment **Grade 3 laboratory abnormality** that is: (a) clinically significant or (b) at least possibly related to study treatment **Grade 4 laboratory abnormality** that is at least possibly related to study treatment	Delay study treatment for up to 21 days	
	If the event resolves to Grade <2 or the patient's baseline level within 21 days:	
	• **First occurrence:**	**Then**, resume study treatment, at the discretion of the investigator. Dose reduction is not required.
	• **Second occurrence of the same event:**	**Then**, resume study treatment at a reduced dose, as shown in Table JVDE.2.
	If the event does not resolve Grade <2 or the patient's baseline level within 21 days	**Then**, discontinue study treatment.
Any other Grade 4 clinical AE that is at least possibly related to study treatment	Discontinue study treatment.	

Abbreviation: AE = adverse event.

9.5. Blinding

This is a double-blind study. To preserve the blinding of the study, ramucirumab will be visibly indistinguishable from placebo, and unblinding will not occur at disease progression. Additionally, no anticipated or identified toxicity of ramucirumab would potentially unblind investigators to treatment assignment. Unblinding of the study team will occur after the reporting database is validated and locked for final statistical analysis.

Upon overall study completion (see Section 8.1.1), investigators may unblind patients to study treatment assignment.

Efficacy information will be shared with sites after study completion. Treatment assignment will be blinded in the reporting database until that database is locked for data analysis. This will ensure unblinded aggregate efficacy results are not available until the time of final data analysis.

Interim analyses will be prepared by an independent statistical analysis center (SAC). Access to unblinded data and documents will be controlled by restricting access to the data/documents to members of an independent data monitoring committee (IDMC). Members of the IDMC will be permitted to access unblinded data only at the time(s) of the interim analyses. Any changes to this unblinding plan may be described in a protocol amendment, the SAP, and/or a separate unblinding plan document. See Section 12.2.13 for further details about the planned interim analyses.

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 for medical management of the event. 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 oncology studies 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 treatment or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have a 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 on the CRF at each visit. 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.

A list of restricted and excluded medications is provided in Attachment 9. No chemotherapy, experimental medications, other systemic anticancer therapy, immunotherapy, hormonal cancer therapy, or curative surgery or procedures for cancer will be permitted while patients are on study treatment.

9.6.1. Supportive Care

Patients should receive full supportive care in accordance with local practice as judged appropriate by the investigator. 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.

Treatment and management of chronic viral hepatitis is left to the investigator's discretion or local practice. For patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, antiviral therapy before and/or throughout the course of treatment may be considered to reduce the risk of viral reactivation.

If the investigator is unsure of whether a therapy should be regarded as supportive care, the investigator should consult with the Lilly CRP. Use of any supportive care therapy should be reported on the CRF.

9.7. Treatment Compliance

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

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations. Study procedures related to efficacy, safety, health outcomes/quality of life measures, 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

Within 4 weeks before the first dose of study treatment (within 3 weeks prior to randomization), baseline tumor measurements will be performed on each patient. Computed tomography (CT), including spiral CT scans and magnetic resonance imaging (MRI) are the preferred methods of measurement.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses, but cannot be used to assess response according to RECIST 1.1 (Attachment 7).

Computed tomography scan of the chest and contrast-enhanced CT or MRI of the abdomen (abdominal imaging should include intravenous contrast) should be performed at baseline. If there is concern about radiation exposure from CT, MRI may be used instead of CT. If intravenous CT contrast material is contraindicated because of hypersensitivity reaction, then chest CT or MRI (without contrast) and MRI of the abdomen with intravenous (gadolinium) contrast is required. Disease should be recorded and metastases identified at baseline.

During study treatment, perform tumor assessment and imaging as follows:

- every 6 weeks (±3 days) for the first 6 months after randomization, and
- every 9 weeks (±3 days) thereafter until the patient has radiographic PD or dies, whichever occurs first.

Except when deemed not feasible in the opinion of the investigator because of the patient's clinical status, imaging studies and tumor assessments will be performed as scheduled, even if study treatment is delayed. If disease in the chest was not identified at baseline, further radiographic assessment of the chest is not required unless clinically indicated.

The method of tumor assessment used at baseline must be used consistently throughout the study until death or study completion.

10.1.2. Efficacy Assessments during the Postdiscontinuation Follow-Up Period

Postdiscontinuation follow-up will be conducted as described in the Study Schedule (Attachment 1). The method of tumor assessment used at baseline must be used consistently throughout the study until death or study completion.

For patients who discontinue study treatment for reasons other than radiographic PD, the investigative sites will continue to monitor these patients and evaluate tumor response as follows:

- every 6 weeks (± 3 days) for the first 6 months after randomization, and
- every 9 weeks (± 3 days) thereafter until the time of radiographic disease progression, death, or study completion, whichever occurs first.

After the patient has radiographic disease progression, radiologic tests are no longer required, and the patient will be followed for approximately every 60 days (±7 days) until death or study completion, whichever occurs first.

During long-term follow-up, patients will be contacted every 60 days (±7 days) to obtain information about survival and detailed information on any postdiscontinuation systemic anticancer therapy. Survival follow-up may be done by telephone or site visit and will continue until the patient's death, withdrawal of consent, or study completion, as defined in Section 8.1.1.

10.1.3. Efficacy Assessments during the Continued Access Period

During the continued access period, efficacy assessments (frequency and type of assessments) will be performed at the discretion of the investigator, based on the standard of care.

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.

10.1.4. Primary Efficacy Measure

Overall survival will be measured from the date of randomization to the date of death from any cause. For each patient who was not known to have died as of the data-inclusion cutoff date for overall survival analysis, OS will be censored on the last date the patient was known to be alive.

10.1.5. Secondary Efficacy Measures

The following secondary efficacy measures (Table JVDE.5) will be collected at the times shown in the Study Schedule (Attachment 1).

Table JVDE.5. Secondary Efficacy Endpoints

Endpoint	Definition
Progression-free survival	The time from the date of randomization to the date of first observation of objective progression or death from any cause. Details about PFS censoring rules, subgroup and sensitivity analyses will be stated in the statistical analysis plan.
Time to radiographic progression	The time from the date of randomization to the date of first observation of objective progression.
Objective response rate	The percentage of patients who achieve a best overall response of CR or PR. Best overall response will be classified based on the overall responses assessed by study investigators according to RECIST Version 1.1.

Abbreviations: CR = complete response; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors.

10.2. Health Outcome/Quality of Life Measures

The assessment of patient-reported outcomes, including disease-specific symptoms and health status, will be assessed using the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L). The instruments will be administered together with the FHSI-8 presented first, followed by presentation of the EQ-5D-5L. Patients will complete the instruments only if the instruments have been translated into a language in which the patient is fluent and the translation has been validated. Refer to the Study Schedule (Attachment 1) for the specific timing of these assessments.

10.2.1. Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8)

The FHSI-8, a self-administered questionnaire with specific focus regarding the most frequent and concerning symptoms experienced by patients with hepatobiliary malignancies, involves a 5-point assessment for 8 symptoms, including symptoms more specific to hepatobiliary cancer (jaundice, stomach pain/discomfort) and symptoms associated with generalized advanced/metastatic malignancy (weight loss, fatigue; Yount et al. 2002). The 8 items on the FHSI-8 were drawn from the larger FACT-G and 18-item hepatobiliary subscale (Cella et al. 1993; Heffernan et al. 2002). These items were selected based on relative clinical importance ratings provided by a multinational group of 95 hepatobiliary cancer specialists. Results from the 8-item FHSI-8 correlated significantly with the larger FACT-G and hepatobiliary subscale instruments and demonstrated internal consistency, reliability, and convergent validity. Additionally, the FHSI-8 was utilized in the multinational REACH study to demonstrate a delay in time to symptomatic deterioration in patients with elevated baseline AFP treated with ramucirumab versus placebo. The FHSI-8 was also included in the multinational SHARP study comparing sorafenib versus placebo in patients with advanced, unresectable HCC (Llovet et al. 2008b).

10.2.2. EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire

The EQ-5D-5L is a nonspecific and standardized instrument for use as a measure of self-reported health status (EuroQol Group 1990; Herdman et al. 2011). Patients will complete the 5-level (no problems, slight problems, moderate problems, severe problems, and extreme problems), 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) questionnaire concerning their current health state. A unique EQ-5D-5L health state is defined by combining 1 level from 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).

The EQ-5D-5L should be completed by the patient following completion of the FHSI-8, before any extensive contact or consultation with study site personnel.

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(s) that seems unusual, even if this event(s) may be considered an unanticipated benefit to the patient.

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the study schedule (Attachment 1) and the continued access study schedule (Attachment 2). Table JVDE.6 presents a summary of AE and SAE reporting guidelines for every period of this study – at baseline, during study treatment, during short- and long-term follow-up, and during continued access. Table JVDE.6 also shows the database or system is used to store AE and SAE data.

Table JVDE.6. Adverse Event and Serious Adverse Event Reporting Guidelines

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

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

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 event associated with the use of a drug in humans, whether or not it is considered related to that drug.

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

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

Cases of pregnancy that occur during maternal or paternal exposures to ramucirumab or placebo should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

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

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

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

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

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

- **Probably related**: a direct cause and effect relationship between 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 or study procedure.

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

The CTCAE Version 4.0 (NCI 2009) will serve as the reference document for choosing appropriate terminology for, and grading the severity of all AEs and other symptoms. For AEs without matching terminology within CTCAE Version 4.0, the investigator will be responsible for selecting the appropriate system organ class and assessing a severity grade based on the intensity of the event.

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

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

10.3.1.1. Adverse Events of Special Interest for Ramucirumab

Table JVDE.3 presents the criteria for dose modifications applicable if the patient experiences an AESI. Contact the Lilly CRP if questions arise concerning AESIs.

10.3.1.1.1. Infusion-Related Reactions

Infusion-related reaction is considered an AESI because it has been observed in association with other approved and investigational therapeutic monoclonal antibodies and has also been observed in studies with ramucirumab. In REACH, the previous Phase 3 study of ramucirumab

in HCC, the incidence of any-grade IRRs or Grade 3 IRRs was low. No Grade 4 or Grade 5 IRRs were observed.

Patients should be closely monitored for signs and symptoms indicative of an IRR from the initiation of the infusion until after the end of the infusion, in an area where resuscitation equipment and other agents (such as epinephrine and corticosteroids) are readily available. A 1-hour observation period following the ramucirumab infusion is mandatory for the first 2 cycles. If a patient shows no evidence of an IRR in the first 2 cycles of ramucirumab, no observation period is required for subsequent treatment cycles. In the event an IRR occurs thereafter, the 1-hour observation period should be reinstituted.

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

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

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

Dose-modification guidelines for patients experiencing an IRR are provided in Table JVDE.3.

10.3.1.1.2. Hypertension

An increased incidence of severe hypertension (CTCAE Grade 3) has been reported in patients receiving ramucirumab. In most cases, hypertension was controlled using standard antihypertensive treatment. In REACH, no Grade 4 or Grade 5 hypertension events were observed.

Monitoring of blood pressure is required during ramucirumab therapy. Every attempt should be made to control blood pressure to systolic blood pressure (BP) <140 mm Hg and diastolic BP <90 mm Hg prior to starting treatment with ramucirumab/placebo.

Dose-modification guidelines for patients experiencing hypertension are provided in Table JVDE.3.

10.3.1.1.3. Proteinuria

Proteinuria is an adverse effect for all therapies targeting the VEGF/VEGF Receptor 2 pathway. Proteinuria has been associated with ramucirumab in clinical studies, including REACH. The majority of events were Grade 1 or 2. In REACH, no Grade 4 or Grade 5 proteinuria events were observed.

Monitoring for the development or worsening of proteinuria during ramucirumab therapy is required. Prior to each dose of study treatment, the patient's urine protein must be ≤2+ on dipstick or routine urinalysis or <2 g on 24-hour urine collection (Table JVDE.1).

Dose-modification guidelines for patients experiencing proteinuria are provided in Table JVDE.3.

10.3.1.1.4. Thromboembolic Events

10.3.1.1.4.1. Arterial Thromboembolic Events

Serious, sometimes fatal arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, have been reported in clinical trials of ramucirumab. In REACH, no Grade ≥3 ATEs occurred in the ramucirumab arm.

Discontinue study treatment if the patient experiences a Grade 3 or 4 ATE (Table JVDE.3).

10.3.1.1.4.2. Venous Thromboembolic Events

Venous thromboembolic events (VTEs) have been reported in clinical studies investigating ramucirumab, particularly in the context of metastatic disease or in areas adjacent to implanted venous access devices. In REACH, the overall incidences of VTEs was low, and there were no Grade 4 or Grade 5 VTEs observed in the ramucirumab arm.

Most VTEs lack early warning signs; therefore, awareness and prompt treatment is important, especially in patients with risk factors and/or previous history of VTEs (Chen and Cleck 2009; Suter and Ewer 2013).

Discontinue study treatment if the patient experiences a Grade 3 or 4 VTE (Table JVDE.3).

10.3.1.1.5. Bleeding/Hemorrhage

Serious hemorrhagic AEs have been reported from some clinical studies investigating ramucirumab. In REACH, overall bleeding events (any grade) were observed at a higher incidence in the ramucirumab arm (32.5%) compared with the placebo arm (19.9%). However, no difference was observed in the incidence of Grade ≥3 events (ramucirumab arm, 6.1%; placebo arm, 7.6%). The most frequently reported bleeding event in the ramucirumab arm was epistaxis, and its incidence was higher (13.7%) compared with the placebo arm (6.2%). No Grade ≥3 epistaxis events occurred in either treatment arm.

Discontinue study treatment if the patient experiences Grade 3 or 4 bleeding (Table JVDE.3).

10.3.1.1.6. Gastrointestinal Perforation

An infrequent incidence of gastrointestinal (GI) perforations has been associated with some antiangiogenic therapeutic agents, most specifically in the context of colorectal cancer and in advanced ovarian cancer. Gastrointestinal perforation has been reported from clinical studies investigating ramucirumab, although no events of GI perforation were observed in REACH.

Discontinue study treatment if the patient experiences a GI perforation (Table JVDE.3).

10.3.1.1.7. 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).

Across the clinical program to date, 2 cases of RPLS have been reported. Both cases occurred in the study evaluating ramucirumab in combination with chemotherapy for patients with metastatic colorectal cancer. No RPLS events were observed in REACH.

Symptoms of RPLS most often include generalized seizures, headache, delirium, and cortical blindness, although these may vary significantly and occasionally include focal neurological deficits (Hinchey et al. 1996; Garg 2001; Lee et al. 2008). MRI represents the most reliable method for diagnosis (Lee et al. 2008).

Discontinue study treatment if the patient experiences RPLS (Table JVDE.3).

10.3.1.1.8. Congestive Heart Failure

An increased risk of congestive heart failure (CHF) has been associated with some antiangiogenic therapeutic agents, particularly in patients previously treated with anthracyclines. A small number of CHF events (including fatal) were also reported in patients who had received ramucirumab after prior treatment with anthracyclines. In REACH, no events of CHF were observed in the ramucirumab arm.

Patients with risk factors should be closely monitored for signs and symptoms of CHF. Caution should be exercised when treating patients with clinically significant cardiovascular disease, such as preexisting coronary artery disease or CHF.

Discontinue study treatment if the patient experiences any Grade 3 or 4 events consistent with CHF (Table JVDE.3).

10.3.1.1.9. Fistula Formation

Fistula formation has been associated with antiangiogenic agents and patients may be at an increased risk for the development of fistula when treated with ramucirumab. Fistula has been reported from clinical studies investigating ramucirumab, although no events of fistula were observed in REACH.

Discontinue study treatment if the patient experiences a fistula (Table JVDE.3).

10.3.1.1.10. Surgery and Impaired Wound Healing

Because ramucirumab is an antiangiogenic therapy, it may have the potential to adversely affect wound healing. Ramucirumab did not impair wound healing in a study conducted in animals; however, the impact of ramucirumab on serious or nonhealing wounds has not been evaluated in humans. In REACH, no wound healing complications were observed in the ramucirumab arm.

Withhold study treatment prior to any planned surgery (Table JVDE.3). In the event of postsurgical or other wound complications, delay study treatment until the wound is fully healed.

After surgery, resume study treatment based on clinical judgment. Delay ramucirumab dosing (for up to 21 days) in the case of any post-surgical or other wound complications until the wound is fully healed.

10.3.1.1.11. Liver Failure and Other Significant Liver Injury

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients with advanced HCC receiving ramucirumab.

In REACH, the incidence of any-grade liver failure / liver injury events, including clinical and laboratory events, was higher in the ramucirumab arm (50.5%) compared with the placebo arm (37.3%). Any-grade clinical events reported at a higher rate in the ramucirumab arm included hepatic encephalopathy and ascites. There was no difference in the incidence of Grade 3/4 liver failure/injury in the ramucirumab arm (19.1%) compared with the placebo arm (22.5%). No Grade 5 events of hepatic encephalopathy or ascites were observed.

Discontinue study treatment if the patient experiences hepatic encephalopathy and/or hepatorenal syndrome (Table JVDE.3).

10.3.1.2. Serious Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

10.3.1.3. Suspected Unexpected Serious Adverse Reactions

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

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiograms

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

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

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

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

10.3.2.2. Echocardiogram or Multiple-Gated Acquisition Scan

An echocardiogram or multiple-gated acquisition scan will be performed according to the study schedule (Attachment 1). Additional evaluations are not required but should be performed in the setting of cardiac symptoms, at the discretion of the investigator.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study. The IDMC will also conduct periodic safety reviews as described Section 12.2.13. In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the IDMC will be unblinded.

All deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to ensure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or clinical AE is deemed serious, unexpected, and possibly related to study drug, only Lilly Global Patient Safety 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.

If a patient experiences elevated ALT >5× ULN and/or elevated total bilirubin >2× ULN, clinical and laboratory monitoring may be initiated, at the discretion of the investigator. 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.

10.3.4. Complaint Handling

Lilly collects product complaints on ramucirumab 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 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/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

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

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

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study. Attachment 2 lists the schedule for sample collections during the continued access period.

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.

10.4.1. Samples for Study Qualification and Health Monitoring

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

Eligibility and treatment decisions will be based on results of tests performed locally (Attachment 3). All tests that require central laboratory processing must be collected and submitted to the central laboratory. Unscheduled laboratory tests do not require central laboratory processing except in the case of an IRR, wherein both immunogenicity and PK samples would be sent to the central laboratory for processing. If hepatic monitoring is initiated (Section 10.3.3), then these samples will also be sent to the central laboratory for processing (Attachment 4).

Baseline serum AFP testing must be determined by the local laboratory using a legally marketed AFP assay for the region in which the site is located.

Investigators must document their review of each laboratory safety report.

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

10.4.2. Stored Samples for Translational Research

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to ramucirumab, angiogenesis, and the disease state. The study will analyze the clinical correlation between biomarkers and

clinical outcome and may be used for related research methods or validation of diagnostic tools or assays.

Samples for translational research will be collected at the times specified in Attachment 8.

The following samples are mandatory (required) for biomarker research, except as indicated otherwise:

- Plasma for biomarkers (see Section 10.4.2.2)
- Whole blood for DNA sample (pharmacogenetic analysis) (see Section 10.4.2.3)

For these mandatory samples, all sites are required to participate in the translational research portion of the study, and patient participation in the translational research portion of the study is mandatory, unless restricted by local regulations.

10.4.2.1. Archived Tumor Tissue

An optional archived tumor tissue sample will be collected, if available, from all patients, and will be examined for markers that may include, but are not limited to, those related to HCC, angiogenesis, and/or ramucirumab (Attachment 8). Mutation profiling, copy number variability, gene expression, DNA sequencing, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

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 block or unstained slides. Pathology notes accompanying archival tissue may also be requested.

The archived tumor tissue samples will be stored for a maximum of 15 years after the last patient visit for the study; any samples remaining at that time will be destroyed. Paraffin-embedded blocks will be returned to the site; slides will not be returned.

10.4.2.2. Plasma Samples

Plasma samples may be used for research on pathways associated with HCC, angiogenesis, the mechanism of action of ramucirumab, and may also be used for related research methods or validation of diagnostic tools or assays. [redacted]

Plasma samples will be collected for potential biomarker research unless precluded by local regulations or IRB policy. The schedule for collection of these samples is provided in Attachment 8.

Samples will be identified by the patient number (coded) and stored at a facility selected by Lilly or its designee for up to 15 years after the last patient visit for the study.

10.4.2.3. Whole Blood Sample for DNA Collection

A blood sample will be collected for pharmacogenetic analysis where local regulations and IRBs allow (Attachment 8). This sample is not being collected to create a biobank for conducting unspecified disease or population genetic research either now or in the future.

Samples may be used to investigate variable response to ramucirumab and to investigate genetic variants thought to play a role in HCC. Assessment of variable response may include evaluation of adverse events or differences in efficacy. [redacted]

Samples will be retained for a maximum of 15 years after the last patient visit, or as local regulations and IRB require, for the study at a facility selected by Lilly. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available. Any samples remaining at the end of the retention period will be destroyed according to a process consistent with local regulations.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. Existing approaches may include whole genome or exome sequencing, genome-wide association studies, candidate-gene studies, and epigenetic analyses. Regardless of the technology utilized, genotyping data generated will be used only for the specific research scope described in this protocol.

10.4.3. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against ramucirumab at specified time points and in the event of an IRR (Attachment 8). Refer to Attachment 2 for the timing of immunogenicity testing during the continued access period.

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

To interpret the results of immunogenicity, the concentration of ramucirumab in the blood will also be measured at the same time points (Attachment 8).

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

10.4.4. Samples for Drug Concentration Measurements (Pharmacokinetics)

Blood samples will be collected from all study patients to assess ramucirumab concentrations in serum as specified in Attachment 8. Instructions and supplies for the collection, handling, and shipping of samples will be provided by Lilly or the central laboratory.

In the event of an IRR, every attempt should be made to collect blood samples for anti-ramucirumab antibody and serum ramucirumab concentration determination at those given time points, as described in Attachment 8. Refer to Attachment 2 for the timing of blood sample collection during the continued access period.

Serum concentrations of ramucirumab will be analyzed at a laboratory designated by the sponsor using a validated method. The samples will be stored in the United States.

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

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 IRBs 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, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary objective of this study is to compare ramucirumab versus placebo in terms of OS in patients with advanced HCC after intolerance or progression on prior sorafenib. The sample size was determined based on the following assumptions:

- hazard ratio (treatment/control) of 0.67, with median OS of 4.5 months in the placebo arm and 6.7 months in the ramucirumab arm
- the randomization ratio is 2:1 (ramucirumab:placebo)
- the overall significance level will be controlled at 1-sided 0.025 (2-sided 0.05)
- the Type II error rate is 20%; that is, the statistical power of the trial is set to 80%

Under the assumptions above, the final analysis will be performed when at least 221 deaths have been observed. Therefore, the study will randomize approximately 279 patients (that is, 20% censoring rate including dropouts, with approximately 186 patients randomized to the ramucirumab arm [Arm A] and 93 patients randomized to the placebo arm [Arm B]).

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

Efficacy and safety analyses will be performed using SAS® version 9.2 or later (SAS Institute, Cary, NC, USA), or comparable software. A complete description of data handling rules and planned statistical analyses will be detailed in a separate SAP prior to conducting any planned analysis.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the SAP.

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

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

12.2.1.1. Analysis Populations

The following populations will be defined for this study:

Intention-to-Treat (ITT) population: will include all randomized patients. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized, and not by actual treatment received. This population will be used for all baseline, efficacy, and health outcome analyses.

Per-Protocol population: will include all patients who are randomized and treated and do not have any major protocol violations that could potentially affect the efficacy conclusions of the study. This population will be defined in detail in the SAP prior to database lock, and will be used for sensitivity analyses of OS and PFS; other efficacy endpoints may also be analyzed.

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

12.2.2. Patient Disposition

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

12.2.3. Patient Characteristics

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

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

12.2.4.1. Postdiscontinuation Therapy

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

12.2.5. Treatment Compliance

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

12.2.6. Primary Efficacy Endpoint

Overall survival time is defined as the time from randomization until death due to any cause. The analysis of OS will be based on stratified log-rank test, stratified by randomization strata as recorded in the IWRS. Overall survival curves, the median with 95% CI and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata as recorded in the IWRS. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

In addition, the following sensitivity analyses will be performed for OS:

- unstratified log-rank test and Cox models
- analysis of the per-protocol population
- univariate and multivariate Cox regression model to explore potential prognostic and/or predictive factors
- additional sensitivity analyses may be specified in the SAP

12.2.7. Secondary Efficacy Endpoints

Progression-free survival (PFS)

- The analysis of PFS will be based on stratified log-rank test, stratified by randomization strata (IWRS).
- PFS survival curves, the median with 95% CI and survival rates at various time points for each treatment group will be estimated using Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model, stratified by randomization strata as recorded in the IWRS.
- The following sensitivity analyses will be performed for PFS:
  - unstratified log-rank test and Cox models
  - analysis for the per-protocol population
  - analysis including both radiographic and clinical progressions as PFS events
  - sensitivity analysis for various PFS censoring rules (for example, post-discontinuation systemic anticancer therapy, missing 2 or more tumor assessments prior to PD/death, etc.; more details will be specified in the SAP)
  - Univariate and multivariate Cox regression model will be used to explore potential prognostic and/or predictive factors.
  - Additional sensitivity analyses may be specified in the SAP.

Objective response rate (ORR) and disease control rate (DCR)

- The best overall response will be determined using RECIST Version 1.1 (Attachment 7).
- The ORR will be calculated as the number of patients who achieve a best overall response of complete response (CR) or partial response (PR), divided by the total number of patients randomized to the corresponding treatment group (ITT population). The DCR will be calculated as the number of patients who achieve a best overall response of CR, PR, or stable disease, divided by the total number of patients randomized to the corresponding treatment group (ITT population). Patients who do not have a tumor response assessment for any reason are considered as nonresponders and are included in the denominator when calculating the response rate. The ORR or DCR with 95% CI observed in each treatment group will be summarized and compared using the Cochran-Mantel-Haenszel test adjusting for the randomization strata.

Time to disease progression (TTP)

- The treatment groups will be compared using the stratified log-rank test and the stratified Cox regression model, and the survival curves will be estimated using the Kaplan-Meier methodology.

- TTP will be analyzed for all randomized patients (ITT population). Additional sensitivity analyses using alternative censoring rules may be performed.

Time to deterioration in ECOG PS

- Time to deterioration in ECOG PS is defined as the time from the date of randomization to the first date observing ECOG PS ≥2 (that is, deterioration from baseline status of 0 or 1).
- The survival curves and median with 95% CI will be estimated using the Kaplan-Meier methodology and will be compared using Cox regression model and log -rank test.

A gatekeeping approach for selected secondary endpoints will be applied so as to protect the study-wise type I error rate and to enable inferential statements; each hypothesis is inferentially tested only if each of the preceding hypotheses were rejected. The sequential order of the confirmatory testing in the ITT population will be: OS, PFS, time to deterioration in FHSI-8 (defined in Section 12.2.10.1), and time to deterioration in ECOG PS. Secondary endpoints will be analyzed at the same level of significance as OS.

Additional exploratory analyses may be performed as deemed appropriate.

12.2.8. Pharmacokinetic and Immunogenicity Analyses

Serum concentrations of study drug (ramucirumab or placebo) prior to infusion (trough concentration) and at 1 hour after the end of the infusion (approximately peak concentration) will be summarized using descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate. Relationships between ramucirumab exposure and measures of efficacy and safety will be explored. Details will be described in the SAP.

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

A limited number of preidentified individuals may gain access to the unblinded PK data prior to final database lock in order to initiate the population PK model development processes for final analyses. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

12.2.9. Exploratory Biomarker Analyses

Biomarker results will be summarized and analyzed for correlations with clinical outcomes.

12.2.10. Health Outcome/Quality of Life Analyses

The main analysis will be conducted in the ITT population as defined in Section 12.2.1.1. Exploratory analyses of PROs may be performed on subpopulations as appropriate.

12.2.10.1. Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8)

FHSI-8 scores and their change from baseline will be summarized descriptively at each assessment time point. The change from baseline in FHSI-8 will be compared to determine whether statistically significant differences exist between the ramucirumab and placebo arms. Completion compliance of the FHSI-8 questionnaires will be described by assessment time point (including baseline, on-study, and short-term follow-up) by the number and percentage of patients who filled out a questionnaire (per patient, at least 1 question answered) over number of patients who are expected to complete the questionnaire at that time point. Reasons for noncompliance will be summarized. Analyses will be described in detail in the SAP.

Time to deterioration in FHSI-8

- Time to deterioration in FHSI-8 is defined as the time from the date of randomization to the first date observing a decrease of ≥3-points from baseline.
- The survival curves and median with 95% CI will be estimated using the Kaplan-Meier methodology and will be compared using Cox regression model and log -rank test.

12.2.10.2. EuroQol 5-Dimension 5-Level (EQ-5D-5L)

For the EQ-5D-5L, a health profile will be generated by visit and by treatment from summary statistics, including number of patients and proportion of categorical responses for the 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). The visual analogue scale (VAS) will be scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the patient's self-report concerning how bad or how good their health was during that day. The 5-dimension, single-item, 5-level responses will be summarized. Descriptive statistics for the index and VAS will be calculated. Completion compliance of the EQ-5D-5L questionnaires will be described by assessment time point (including baseline, on-study, and short-term follow-up) by the number and percentage of patients who filled out a questionnaire (per patient, at least 1 question answered) over number of patients who are expected to complete the questionnaire at that time point. Reasons for noncompliance will be summarized.

12.2.11. Safety Analyses

All safety summaries and analyses will be based on the safety population as defined in Section 12.2.1, unless otherwise indicated, and include:

- Adverse events will be summarized by MedDRA System Organ Class and Preferred Term (PT), classified from verbatim terms. The incidence and percentage of patients with at least 1 occurrence of a PT will be included, according to the most severe CTCAE grade. Causality (relationship to study drug), action taken, and outcome will be summarized separately. Duration of AEs will be determined and included in the listings.
- Study drug exposure will be summarized for each arm with following variables: number of infusion, number of cycles, duration of therapy, cumulative dose, dose intensity, and relative dose intensity.

- Laboratory results will be classified according to the NCI-CTCAE, Version 4.0. Incidence of laboratory abnormalities will be summarized.

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

12.2.12. Subgroup Analyses

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

12.2.13. Interim Analyses

An IDMC will be established as an oversight mechanism to monitor overall study conduct. The membership, roles and responsibilities for the IDMC are defined in the IDMC Charter.

Regular safety reviews will be conducted by the IDMC. There will be no prespecified rules for stopping or modifying the trial due to safety concerns. The IDMC members will review unblinded safety data at each interim analysis to determine whether there are sufficient safety concerns to justify modifying the study or the termination of study treatment and/or enrollment. The first 2 safety interim analyses are planned to be performed when approximately 50 and 150 patients have received 3 cycles of study treatment, died, or discontinued study treatment. Thereafter, safety review will be conducted twice annually, or as requested by the IDMC.

No efficacy interim analysis is planned for this study.

Only the IDMC is authorized to evaluate unblinded interim analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients. Details on the process flow/communication plan are provided in the IDMC Charter.

Patient enrollment will continue during data assessment by the IDMC.

12.3. Ethical Review

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

Documentation of IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites.

The study site's IRB 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
- the ICF
- relevant curricula vitae

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. The ICF will be used to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study as well as his or her desire to participate in the study.

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

13.2. Regulatory Considerations

This study will be conducted in accordance with:

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

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

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

An identification code assigned by the IWRS 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.

13.2.1. Investigator Information

Physicians with experience in managing and treating HCC patients will participate as investigators in this clinical trial.

13.2.2. 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.

13.2.3. 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 JVDE Study Schedule

Study Procedure	Protocol Reference	Prior to Randomization			Treatment Period (Begins ≤7 days after randomization)			Postdiscontinuation Follow-Up[a]		
								Short-Term[b]		Long-Term
		≤21 days	≤14 days	≤7 days	Every Cycle (q2w)	Every 3rd Cycle[z]	Every 6 weeks (q6w)	Day 1-7	Day 30	
Visit		**0**			**1 to 99**			**801**		**802-8XX**
Pretreatment/Clinical Evaluations										
Informed consent	Sec 10	X[c]								
Inclusion/exclusion criteria	Sec 7	X								
Medical history and demographics[d]	Sec 10.3.1	X								
ECG[e]	Sec 10.3.2.1	X							X	
MUGA scan or echocardiogram[e]	Sec 10.3.2.2	X							X	
ECOG performance status	Att 5		X		X[f]			X[y]	X	
Concomitant medication/therapy[g]	Sec 9.6		X		X			X[y]	X	
Physical examination[h]			X[i]		X				X	
Vital signs[j]			X		X				X	
AE collection; CTCAE grading	Sec 10.3.1	X	X	X	X			X[y]	X	X[k]
Laboratory Evaluations[l]										
Hematology profile[m]	Att 3		X		X				X	
Coagulation profile[n]	Att 3		X		X				X	
AFP[o]	Sec 10.4.1 and Att 3		X			X		X[y]		
Chemistry profile[p]	Att 3		X		X				X	
Urinalysis[q]	Att 3		X		X				X	
Pregnancy test[r]	Att 3			X		X				
Hepatitis B and C panels[s]	Att 3	X								
Thyroid Function	Att 3	X							X	
Immunogenicity	Att 8									
Pharmacokinetics	Att 8									
Exploratory biomarker research	Att 8									

Study Procedure	Protocol Reference	Prior to Randomization			Treatment Period (Begins ≤7 days after randomization)			Postdiscontinuation Follow-Up[a]		
								Short-Term[b]		Long-Term
		≤21 days	≤14 days	≤7 days	Every Cycle (q2w)	Every 3rd Cycle[z]	Every 6 weeks	Day 1-7	Day 30	
		0			1-99			801		802-8XX
Efficacy Assessments										
Survival data and PDT	Sec 10.1.2							X[t,y]	X[t]	X[t]
Imaging/tumor assessment[i,u]	Sec 10.1	X					X[u]		X[v]	X[v]
PRO measures[w]	Sec 10.2		X				X[w]	X[y]		
Administer Study Treatment	Sec 9				X[x]					

Abbreviations: AE = adverse event; AFP = alpha-fetoprotein; Att = Attachment; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQol 5-dimension 5-Level; FHSI-8 = Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8; ICF = informed consent form; IRB = institutional review board; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PDT = postdiscontinuation anticancer therapy; PK = pharmacokinetics; PRO = patient-reported outcome; q2w = every 2 weeks (14 days); q6w = every 6 weeks (42 days); SAEs = serious adverse events; Sec = Section.

a Postdiscontinuation follow-up begins on the day after the patient and the investigator agree that the patient will no longer continue study treatment. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

b Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and will last for approximately 30 days (±7 days).

c Written informed consent must be obtained prior to any study-related procedures or evaluations and prior to receiving treatment. If the ICF is revised during the course of the study, re-consenting of patients may be required if deemed necessary by Lilly or the IRB.

d Including patient characteristics, preexisting conditions, historical illnesses, and prior treatment.

e Perform additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator.

f Perform assessment prior to administration of study treatment. A time window of -3 days is permitted for the Cycle 1 Day 1 assessment.

g At baseline, record concomitant medication/therapy received within 30 days prior to randomization. At short-term follow-up, record concomitant medication/therapy received since discontinuation of study treatment.

h The physical examination includes measurement of height (at baseline only) and weight. Measure weight at the beginning of each cycle; recalculate the dose if needed.

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

j Vital signs include blood pressure, pulse rate, and temperature. For the patient's first 2 cycles of study treatment, measure all vital signs at the following time points: (i) immediately prior to the infusion; (ii) after completion of the infusion; and (iii) at the end of the 1-hour postinfusion observation period. For all subsequent cycles, measure blood pressure and pulse prior to the infusion and at completion of the infusion; measure other vital signs as clinically indicated.

k During long-term follow-up, only SAEs that are related to ramucirumab or protocol procedures will be collected. Follow-up should be attempted at regularly scheduled intervals (every 60 days [±7 days]) until death or study completion (whichever occurs first). This follow-up might be a phone call to the patient, her/his family, or local doctor.

l All treatment decisions will be based on local laboratory results.

m Hematology: Baseline assessments can be used for treatment decisions for Cycle 1 Day 1 if the baseline assessments were performed ≤7 days prior to Cycle 1 Day 1. Thereafter, perform ≤3 days prior to administration of study treatment in every cycle, unless more frequent assessment is clinically indicated. In situations where hemoglobin is <9 g/dL (5.58 mmol/L) and/or there are signs or symptoms of bleeding, a hematology profile should be performed weekly until hemoglobin is ≥9 g/dL (5.58 mmol/L) and any bleeding-related signs or symptoms have been resolved or adequately investigated.

n Coagulation: Baseline assessments can be used for treatment decisions for Cycle 1 Day 1 if the baseline assessments were performed ≤7 days prior to Cycle 1 Day 1. Thereafter, perform ≤3 days prior to administration of study treatment in every cycle or as clinically indicated.

o AFP: Collect blood samples for local laboratory and central laboratory testing at the same time. The patient's baseline serum AFP testing must be determined by the local laboratory using a legally marketed AFP assay for the region in which the site is located.

p Chemistry: Baseline assessments can be used for treatment decisions for Cycle 1 Day 1 if the baseline assessments were performed ≤7 days prior to Cycle 1 Day 1. Thereafter, perform ≤3 days prior to administration of study treatment in every cycle or as clinically indicated.

q Urinalysis: Baseline assessments can be used for treatment decisions for Cycle 1 Day 1 if the baseline assessments were performed ≤7 days prior to Cycle 1 Day 1. Thereafter, perform ≤3 days prior to administration of study treatment in every cycle. If dipstick or routine urinalysis indicates proteinuria ≥2+, a 24-hour urine collection must be obtained prior to infusion.

r Required for women of child-bearing potential. A serum pregnancy test is required ≤7 days prior to randomization. During the treatment period, perform a serum or urine pregnancy test ≤2 days prior to treatment or per local regulations and/or institutional guidelines, whichever is more frequent.

s See Attachment 3.

t Follow-up for the collection of survival data and postdiscontinuation systemic anticancer treatment should be attempted every 60 days (±7 days) until death or study completion (whichever occurs first). This follow-up might be a phone call to the patient, her/his family, or local doctor.

u See Attachment 7. Perform imaging studies and tumor assessments, including a CT scan of the chest and a contrast-enhanced CT scan or MRI of the abdomen. If there is concern about radiation exposure from CT, MRI may be used instead of CT. The method of tumor assessment used at baseline must be used consistently throughout the study until death or study completion. During the treatment period, perform every 6 weeks (±3 days) for the first 6 months after randomization and every 9 weeks (±3 days) thereafter until radiographic disease progression, death, or study completion, whichever occurs first. If no chest disease was identified from baseline imaging of the chest, further radiographic assessment of the chest is not required unless clinically indicated.

v Perform every 6 weeks (±3 days) for the first 6 months after randomization and every 9 weeks (±3 days) thereafter until radiographic disease progression, death, or study completion, whichever occurs first.

w The FHSI-8 and EQ-5D-5L are the PRO measures for this study. The instruments should be completed at the beginning of each specified visit, before any extensive contact and consultation with study site personnel because such encounters may bias patient responses. The instruments will be administered together, with the FHSI-8 presented first followed by presentation of the EQ-5D-5L. Administer at baseline. Administer during the treatment period, every 6 weeks (±3 days) after randomization and administer at the beginning of short-term follow-up.

x Treatment should begin within 7 days after randomization. In Cycle 1, administer on Day 1. Thereafter, administer on Day 1 (±3 days) of every cycle.

y The scheduled assessments on Days 1-7 of the short-term follow-up period may also be performed on the same day the patient and the investigator agree that the patient will no longer continue study treatment.

z Cycle 3, 6, 9, 12, etcetera.

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

Visit		Study Treatment During the Continued Access Period	Continued Access Follow-Up [a, b]
		501-5XX	901
Procedure	**Protocol Reference**		
AE collection; CTCAE grading[c]	Sec 10.3.1	X[d]	X[d]
Immunogenicity	Sec 10.4.3	X[d]	X[d]
Pharmacokinetics	Sec 10.4.4	X[d]	X[d]
Administer study treatment	Sec 9	X	

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

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

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

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

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

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

Attachment 3. Protocol JVDE Clinical Laboratory Tests

Clinical Laboratory Tests

Randomization and treatment decisions will be based on local laboratories.

For each local chemistry blood draw, samples for central laboratory shipment should be collected as well.

Hematology: (local laboratory only)	**Clinical Chemistry: (local and central laboratory)[a]**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin concentration	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils[b]	Aspartate aminotransferase (AST)
Lymphocytes	Blood urea nitrogen (BUN) or blood urea
Monocytes	Creatinine
Eosinophils	Calcium
Basophils	Glucose
Platelets	Albumin
Hepatitis B and C panels (local and central laboratory)[a]	**Thyroid Function: (central laboratory only)**
Hepatitis B surface antigen (HBsAg)	TSH and free T4 (to be collected at baseline and short-term follow-up)
Hepatitis B surface antibody (anti-HBs)	
Total hepatitis B core antibody (anti-HBc)	**Pregnancy Test: (local laboratory only)[c]**
Hepatitis B e antigen (HBeAg)	(females of child-bearing potential only)
Hepatitis B e antibody (HBeAb or anti-HBe)	Serum or urine
Hepatitis C antibody	
(central laboratory only)	**Tumor Marker: (local and central laboratory)[a,d]**
Hepatitis B DNA (HBV DNA)	Alpha-fetoprotein (AFP) (assessed in serum)
Hepatitis C RNA (HCV RNA)	
Urinalysis/24 hour urine: (local laboratory only)	
Routine dipstick measurements, and if clinically indicated, microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+ at evaluations, a 24 hour urine collection (to assess protein) must be obtained	
Other: (central laboratory only)	**Coagulation Tests: (local laboratory only)**:
Anti-ramucirumab antibody	Prothrombin time (PT or INR)
Ramucirumab concentrations in serum	Partial thromboplastin time (PTT)

Abbreviations: AFP = alpha-fetoprotein; CRF = case report form: RBC = red blood cells; WBC = white blood cells.

[a] Local laboratory results are to be used for enrollment and dosing decisions. Samples must also still be submitted for testing by Lilly-designated central laboratory but will not be used to make treatment decisions.

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

[c] Perform serum pregnancy test ≤7 days prior to randomization. During the treatment period, perform a serum or urine pregnancy test ≤2 days prior to treatment or per local regulations and/or institutional guidelines, whichever is more frequent.

[d] The patient's baseline serum AFP testing must be determined by the local laboratory using a legally marketed AFP assay for the region in which the site is located.

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

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

Hepatic Monitoring Tests

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

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

[a] Assayed by Lilly-designated laboratory.

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

Attachment 5. Protocol JVDE ECOG Performance Status

ECOG Performance Status

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

Source: Oken et al. 1982.

Attachment 6. Protocol JVDE Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Reference: Cockcroft and Gault 1976.

Attachment 7. Protocol JVDE RECIST Criteria 1.1

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

Measurability of Tumor at Baseline

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

Measurable

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

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

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

Nonmeasurable

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

Special Considerations for Lesion Measurability

Bone lesions:

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

Cystic lesions:

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

Lesions with Prior Local Treatment:

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

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

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

Nontarget Lesions

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

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

Specifications by Methods of Measurement

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

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

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

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

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

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

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

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

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

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

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

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

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

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

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

Evaluation of Nontarget Lesions

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

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

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

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

Evaluation of Best Overall Response

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

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.; PD = progressive disease; NE = inevaluable.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

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

Abbreviations: CR = complete response; PD = progressive disease ; NE = inevaluable.

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

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6 to 8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from randomization.

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

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

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

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 8. Protocol JVDE Pharmacokinetic, Immunogenicity, Pharmacodynamic, and Biomarker Sampling Schedule

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

Schedule for Pharmacokinetic, Immunogenicity, Pharmacodynamic, and Biomarker Sampling

Procedure	Cycle 1		Cycle 2		Cycle 4[a]		Cycle 7[c]		Cycle 10[c]		Short-Term Follow-Up[g]
	Pre-Treatment[d]	Post-Infusion[e]	Pre-Infusion[f]	Post-Infusion[e]	Pre-Infusion[f]	Post-Infusion[e]	Pre-Infusion[f]	Post-Infusion[e]	Pre-Infusion[f]	Post-Infusion[e]	
Pharmacokinetics[h,i]	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity[h,i]	X				X		X				X
Tumor tissue[j]	X										
Plasma	X				X		X				X
Whole blood[k]	X										

Abbreviation: IRR = infusion-related reaction.

[a] Approximately 6 weeks after the first infusion of study treatment. Collect samples only if the patient receives study treatment in Cycle 4.

Footnote b has been deleted.

[c] Collect samples only if the patient receives study treatment in Cycle 7 or Cycle 10.

[d] Obtain samples for pharmacokinetics, immunogenicity, plasma, and whole blood within 7 days prior to the first infusion.

[e] Obtain sample 1 to 1.5 hours after the end of the infusion.

[f] Obtain sample up to 3 days before the infusion.

[g] Obtain sample any time during the short-term follow-up visit.

[h] There is flexibility in the recommended sampling times at the indicated cycles. However, it is essential that the draw dates and draw times are accurately recorded.

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

[j] Collection of tumor tissue is optional. Previously archived formalin-fixed paraffin-embedded tumor tissue obtained from the primary tumor or metastatic site should be provided as a whole block or unstained slides.

[k] A pretreatment blood sample is preferred; however, the whole blood sample for genetic analysis may be collected at a later time point if necessary.

Attachment 9. Protocol JVDE Permitted and Prohibited Concomitant Therapy

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

Therapy	As Needed	Chronic Use	Conditions for Use
Concurrent chemotherapy or biologic response modifiers, or other investigational anticancer agents	no	no	Not permitted
Chronic antiplatelet therapy, including NSAIDs (such as, indomethacin, ibuprofen, naproxen, nimesulide, celecoxib, etoricoxib, and similar agents) or other antiplatelet agents (such as, clopidogrel, ticlopidine, prasugrel, dipyridamole, picotamide, indobufen, anagrelide, triflusal, and similar agents)	no	no	Not permitted[a]
Aspirin	yes	yes	Permitted at doses up to 100 mg/day
Therapeutic dose anticoagulant therapy	yes	yes	Permitted following on-study occurrence of a Grade ≤2 thromboembolic event provided no evidence of portal hypertension (including splenomegaly) or any prior history of variceal bleeding exists
Prophylactic low-dose anticoagulant therapy	yes	yes	Permitted if INR ≤1.5 and PTT ≤5 seconds above ULN
Colony-stimulating factors	yes	no	Follow local guidelines.
Erythroid growth factors	yes	no	Follow local guidelines.
Experimental medicines	no	no	
Radiotherapy	yes	no	Palliative radiotherapy during the study, if clinically indicated, can be considered after consultation with the Lilly CRP.

Abbreviations: CRP = clinical research physician; INR = International normalized ratio; NSAIDs = nonsteroidal anti-inflammatory drugs; PTT = partial thromboplastin time; ULN = upper limit of normal.

[a] Occasional use of NSAIDs is allowed, if used at low dose and limited duration.

Attachment 10. Protocol Amendment I4T-MC-JVDE(c) Summary

Overview and Rationale

Protocol I4T-MC-JVDE (Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ramucirumab and Best Supportive Care (BSC) versus Placebo and BSC as Second-Line Treatment in Patients with Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-Line Therapy with Sorafenib, has been amended. The new protocol, as amended, is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

This amendment removes the interim analysis of efficacy to consolidate to a single final OS analysis with a power of 80% and uses an OS HR assumption of 0.67, resulting a study size reduction from 399 to 279 patients. Although there is reduction in HR assumption from 0.7 to 0.67 with this new study size, these changes result in a study design that is still sufficient to observe a treatment effect consistent with the results observed in the previous Phase 3 study REACH. In REACH a robust and meaningful survival benefit was observed in patients (n=250) with a baseline AFP ≥400 ng/mL (deaths = 215; HR = 0.674; median OS for ramucirumab 7.8 months versus placebo 4.2 months; p=0.0059); the same population as being investigated in REACH-2. The reduction in power from 85% to 80% with the new study size is considered acceptable for a Phase 3 design and decreases the probability of a statistically significant OS benefit that is not clinically meaningful. There continues to be a high unmet need in the treatment of advanced HCC, particularly in patients who have failed sorafenib, and the amended study provides a good chance of a positive outcome and potential new treatment option for this patient population earlier than would be projected with the initial study design and reduces the number of patients necessary to achieve a clinically relevant study outcome.

This amendment also adds further statistical rigor to assess endpoints related to patient-focused outcomes. REACH analyses in patients with a baseline AFP ≥400 ng/mL suggest benefit from ramucirumab treatment in patient symptoms, as assessed by the Functional Assessment Of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8), and in patient functioning, as assessed by Eastern Cooperative Oncology Group performance status (ECOG PS). Collection of FHSI-8 and ECOG PS data has been ongoing in REACH-2 since initial protocol approval (20 February 2015), and in this amendment, time to deterioration in FHSI-8 and time to deterioration in ECOG PS are specifically identified as gated secondary endpoints.

This amendment also clarifies and removes redundancy in the criteria to be met prior to administration of study treatment (Table JVDE.1) by cross referring to Table JVDE.3. Correction to dose modifications for Grade 3 laboratory toxicity (Table JVDE.4) has also been made to align with other ramucirumab studies. These changes pose no additional risks to

patients. This amendment also removes an incorrect footnote indicator in the study schedule (Attachment 1).

The following section shows all changes included in this protocol amendment.

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: 465~~562~~ Enrolled/Randomized: 279~~399~~	**Phase of Development:** 3
Length of Study: approximately ~~29~~ 32 months Planned first patient visit: June 2015 Planned last patient visit: ~~October~~ January 2018~~7~~ Planned interim analysis: ~~Safety only:~~ when approximately 50 and 150 patients have received 3 cycles of study treatment, died, or discontinued study treatment; thereafter, twice per year. ~~Efficacy interim: when approximately 60% (at least 191 events) of planned OS events have been observed.~~	

Objectives: The primary objective of this study is to compare overall survival (OS) for ramucirumab versus placebo in patients with advanced hepatocellular carcinoma (HCC) after intolerance or progression on prior sorafenib treatment.

The secondary objectives of the study are to evaluate: progression-free survival, time to radiographic progression, objective response rate (ORR), safety profile of ramucirumab, ramucirumab pharmacokinetics, immunogenicity of ramucirumab, time to deterioration in Eastern Cooperative Group performance status (ECOG PS), time to deterioration in Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8), and other patient-reported outcome measures of disease-specific symptoms and health-related quality of life.

The exploratory objective of the study is to explore biomarkers relevant to ramucirumab, angiogenesis, and the disease state and to correlate these markers to clinical outcome.

Criteria for Evaluation:

Time to deterioration in ECOG PS is defined as the time from the date of randomization to the first date observing ECOG PS ≥2 (that is, deterioration from baseline status of 0 or 1).

Time to deterioration in FHSI-8 is defined as the time from the date of randomization to the first date observing a decrease ≥3 points from baseline. Survival curves and median with 95% CI will be estimated using the Kaplan-Meier methodology and will be compared using a Cox regression model and log-rank test.

Statistical Methods:

Statistical: The primary objective of this study is to compare ramucirumab versus placebo in terms of OS in patients with advanced HCC after intolerance or progression on prior sorafenib. The sample size of approximately 279~~399~~ patients was determined ~~using a group sequential analysis methodology~~ based on the following assumptions:

- a hazard ratio (HR) of 0.67, with median OS of 4.5 months in the placebo arm and 6.7~~4~~ months in the ramucirumab arm
- 2:1 randomization (ramucirumab:placebo)
- ~~an interim efficacy analysis will be performed after 60% of the expected OS events are observed in the ITT population, with alpha-spending function of gamma (-6)~~
- the overall significance level will be controlled at 1-sided 0.025 (2-sided 0.05)
- the Type II error rate is ~~15~~20%, that is, 80~~5~~% statistical power

Under the assumptions above, the final analysis will be performed after approximately 221~~319~~ deaths have been observed (assuming 20% censoring rate including dropouts).

A gatekeeping approach for selected secondary endpoints will be applied in order to protect the study-wise type I error rate and enable inferential statements; each hypothesis will be inferentially tested only if each of the preceding hypotheses were rejected. The sequential order of the confirmatory testing in the intent-to-treat (ITT) population will be: OS, progression-free survival (PFS), time to deterioration in FHSI-8, and time to deterioration in ECOG PS~~and ORR~~. ~~Secondary endpoints will be analyzed at the same time as OS and at the same level of significance.~~

Interim analyses will be prepared by an independent statistical analysis center. An independent data monitoring committee will monitor the overall study conduct and perform reviews of safety ~~and efficacy~~ data. ~~At the interim efficacy analysis, the Independent Data Monitoring Committee (IDMC) may recommend early discontinuation of the study for unequivocal efficacy.~~

Efficacy: The ~~primary~~ analysis of OS will be based on a stratified log-rank test, stratified by randomization strata as recorded in the Interactive Web Response System (IWRS). OS curves, median OS with 95% confidence interval (CI), and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method. The HR will be estimated using a stratified Cox regression model, stratified by randomization strata as recorded in the IWRS. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint. Sensitivity analyses of OS will include: unstratified log-rank test and Cox models; analysis for the per-protocol population; and univariate and multivariate Cox regression model to explore potential prognostic and/or predictive factors. Additional sensitivity analyses may be specified in the SAP.

Time to deterioration in ECOG PS will be compared between treatment groups. ~~is defined as the time from the date of randomization to the first date observing ECOG PS ≥2 (deterioration from baseline status of 0 or 1).~~ Survival curves and median with 95% CI will be estimated using the Kaplan-Meier methodology and will be compared using a Cox regression model and log-rank test.

6.2. Secondary Objectives

- Time to deterioration in Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8)
- Time to deterioration in Eastern Cooperative Oncology Group performance status (ECOG PS)

- Other p~~P~~atient-reported outcome (PRO) measures of disease-specific symptoms and health-related quality of life

8.1. Summary of Study Design

Study JVDE is a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 study evaluating the efficacy and safety of ramucirumab as a single agent for the treatment of patients with advanced HCC and elevated baseline AFP after intolerance or progression on prior sorafenib therapy. The primary objective is to compare the overall survival of HCC patients treated with ramucirumab versus patients treated with placebo. Patients with a baseline AFP ≥400 ng/mL, based on local laboratory results, who meet all other inclusion/ exclusion criteria, will be enrolled. The study will randomize (in a 2:1 ratio) approximately ~~399~~279 patients with a baseline AFP ≥400 ng/mL to receive ramucirumab 8 mg/kg or placebo administered intravenously once every 14 days in an outpatient setting. All patients will be offered best supportive care (BSC), as determined appropriate by the investigator. Study treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or until other withdrawal criterion is met.

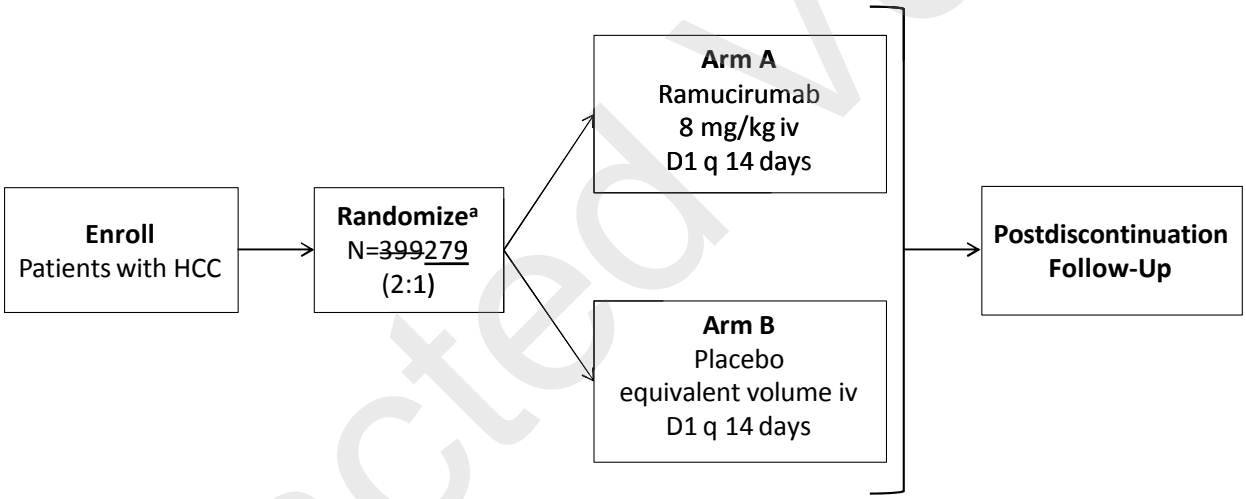

Figure JVDE.1. Illustration of study design.

9.4.1.3. Administration of Study Treatment

Table JVDE.1. Criteria to Be Met Prior to Each Infusion of Study Treatment

Event	Requirement
AESI	Refer to Table JVDE.3
Other clinically significant toxicity or AE related to study treatment, as determined by the investigator	The event must be resolved to CTCAE (Version 4.0) Grade <2 or the patient's baseline level
~~Urine protein~~	• ~~≤2+ on dipstick or routine urinalysis[a]~~ ~~or~~ • ~~<2 g on 24 hour urine collection~~
~~Hypertension~~	• ~~Hypertension is controlled.~~
~~Wound healing~~	• ~~Any wound is fully healed.~~
~~Toxicities and AEs related to study treatment (other than AESIs [see Table JVDE.4])~~	• ~~CTCAE (Version 4.0) Grade <2 or the patient's baseline level, except for clinically insignificant AEs (such as alopecia), as determined by the investigator, are controlled.~~

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CTCAE = Common Toxicity Criteria for Adverse Events (NCI 2009).

~~[a] If urine protein =2+ on dipstick or routine urinalysis, refer to Item 3.a in Table JVDE.3.~~

9.4.2. Dose Modifications

Table JVDE.4. Dose Modifications for Adverse Events That Are Not Adverse Events of Special Interest

AE or Toxicity	Dose Modification	
Grade 3 clinical AE that is at least possibly related to study treatment ~~**Grade 3 laboratory abnormality** that is:~~ ~~(a) clinically significant or~~ ~~(b) at least possibly related to study treatment~~	Delay study treatment for up to 21 days.	
	If the event resolves to Grade <2 or the patient's baseline level within 21 days	**Then**, resume study treatment at a reduced dose, as shown in Table JVDE.2.
	If the event does not resolve Grade <2 or the patient's baseline level within 21 days	**Then**, discontinue study treatment.
Grade 3 or 4 fever that is at least possibly related to study treatment **Grade 3 laboratory abnormality** that is: (a) clinically significant or (b) at least possibly related to study treatment **Grade 4 laboratory abnormality** that is at least possibly related to study treatment	Delay study treatment for up to 21 days	
	If the event resolves to Grade <2 or the patient's baseline level within 21 days:	
	• **First occurrence:**	**Then**, resume study treatment, at the discretion of the investigator. Dose reduction is not required.
	• **Second occurrence of the same event:**	**Then**, resume study treatment at a reduced dose, as shown in Table JVDE.2.
	If the event does not resolve Grade <2 or the patient's baseline level within 21 days	**Then**, discontinue study treatment.

12.1. Determination of Sample Size

The primary objective of this study is to compare ramucirumab versus placebo in terms of OS in patients with advanced HCC after intolerance or progression on prior sorafenib. The sample size was determined ~~using a group sequential analysis methodology~~ based on the following assumptions:

- hazard ratio (treatment/control) of 0.67, with median OS of 4.5 months in the placebo arm and 6.74 months in the ramucirumab arm
- the randomization ratio is 2:1 (ramucirumab:placebo)
- ~~an interim efficacy analysis will be performed after 60% of the expected OS events are observed with alpha-spending function of gamma (-6)~~
- the overall significance level will be controlled at 1-sided 0.025 (2-sided 0.05)
- the Type II error rate is 2015%; that is, the statistical power of the trial is set to 8005%

Under the assumptions above, the final analysis will be performed when ~~a total of~~at least 221319 deaths ~~OS events~~ have been observed. Therefore, the study will randomize approximately ~~399~~ 279 patients (that is, 20% censoring rate including dropouts, with approximately 186~~266~~ patients

randomized to the ramucirumab arm [Arm A] and 93~~133~~ patients randomized to the placebo arm [Arm B]).

12.2.6. Primary Efficacy Endpoint

~~12.2.6.1. Overall Survival~~

Overall survival time is defined as the time from randomization until death due to any cause. The ~~primary~~ analysis of OS will be based on stratified log-rank test, stratified by randomization strata as recorded in the IWRS. Overall survival curves, the median with 95% CI and survival rates at various time points for each treatment group will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). The HR will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata as recorded in the IWRS. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

~~12.2.6.2. Interim and Final Analyses of Primary Endpoint~~

~~The interim efficacy analysis will be prepared by an unblinded, independent SAC statistician and will be reviewed by the IDMC, which may recommend early discontinuation of the study for unequivocal efficacy or continuation of the study.~~

~~The interim efficacy analysis will be conducted when approximately 60% of the planned OS events (at least 191 deaths) have been observed in the ITT population. The planned nominal significance level for the efficacy analysis is 0.0022 (1-sided) or 0.0044 (2-sided) based on an α-spending function of gamma (-6).~~

~~If Lilly declares unequivocal efficacy, the interim analysis will constitute the final (inferential) analysis of OS, and any subsequent analysis based on additional OS events will be considered exploratory. If unequivocal efficacy is not declared, the final OS analysis will be conducted after 319 OS events have been observed in the ITT population. In the latter case, the planned nominal significance level for the final OS analysis is 0.0245 (1-sided) or 0.0490 (2-sided) based on α-spending function of gamma (-6). This α-spending function will be used to determine the actual critical values at the interim and final analyses based on the actual number of observed events at each analysis to ensure that the overall Type I error rate is preserved at the planned 0.025 (1-sided).~~

12.2.7. Secondary Efficacy Endpoints

A gatekeeping approach for selected secondary endpoints will be applied so as to protect the study-wise type I error rate and to enable inferential statements; each hypothesis is inferentially tested only if each of the preceding hypotheses were rejected. The sequential order of the confirmatory testing in the ITT population will be: OS, PFS, time to deterioration in FHSI-8 (defined in Section 12.2.10.1), and time to deterioration in ECOG PS~~and ORR~~. Secondary endpoints will be analyzed at the same level of significance as OS ~~at the interim and final analyses~~.

12.2.8. Pharmacokinetic and Immunogenicity Analyses

A limited number of preidentified individuals may gain access to the unblinded PK data ~~at the interim or~~ prior to final database lock in order to initiate the population PK model development processes for ~~interim analyses or~~ final analyses. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

12.2.10.1. Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8)

Time to deterioration in FHSI-8

- Time to deterioration in FHSI-8 is defined as the time from the date of randomization to the first date observing a decrease of ≥3-points from baseline.
- The survival curves and median with 95% CI will be estimated using the Kaplan-Meier methodology and will be compared using Cox regression model and log -rank test.

12.2.13. Interim Analyses

An IDMC will be established as an oversight mechanism to monitor overall study conduct. The membership, roles and responsibilities for the IDMC are defined in the IDMC Charter. ~~The IDMC will perform unblinded reviews of safety and efficacy data, as described below.~~

~~12.2.13.1. Interim Analysis of Efficacy~~

~~See Sections 12.2.6.2 and 12.2.7.~~

~~12.2.13.2. Interim Analyses of Safety~~

No efficacy interim analysis is planned for this study.

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. Details on the process flow/communication plan are provided in the IDMC Charter.

Attachment 1. Protocol JVDE Study Schedule

Study Procedure
Laboratory Evaluations[l]
Thyroid Function[y]

[redacted]

[redacted]
Approval Date & Time: 24-Apr-2017 20:04:45 GMT
Signature meaning: Approved

[redacted]
Approval Date & Time: 24-Apr-2017 20:52:42 GMT
Signature meaning: Approved