JBAK Protocol (e)

Phase 2 Study of LY2157299 in Patients with Hepatocellular Cancer

NCT01246986

Approval date: 18-Aug-2016

1. Protocol H9H-MC-JBAK(e) Phase 2 Study of LY2157299 in Patients with Hepatocellular Carcinoma

Confidential Information

LY2157299

This is an open-label, multicenter, multicountry, Phase 2 study of LY2157299 in patients with hepatocellular carcinoma. The study design consists of 5 parts. In Part A, patients with alpha-fetoprotein (AFP) ≥1.5x ULN will be randomized to 2 cohorts based on initial dose of LY2157299 to be received (160 or 300 mg/day). In Part B, patients with AFP <1.5x ULN will receive LY2157299 300 mg/day. In Part C, patients with no prior systemic treatment will receive LY2157299 in combination with sorafenib. In Part D, patients will receive LY2157299 in combination with ramucirumab. In Part E, patients who have received at least one prior line of systemic therapy or who have not received prior treatment and are ineligible for sorafenib treatment will receive LY2157299 150 mg BID according to a 21 days on/7 days off schedule.

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Protocol Approved by Lilly: 27 October 2010
Amendment (a) Electronically Signed and Approved by Lilly: 27 February 2012
Amendment (b) Electronically Signed and Approved by Lilly: 05 July 2012
Amendment (c) Electronically Signed and Approved by Lilly: 02 July 2013
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Amendment (e) Electronically Signed and Approved by Lilly on date provided below.

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2. Synopsis

Study Rationale

Transforming growth factor beta (TGF-β) is an important protein that regulates the immune response to tumor cells and metastatic spread of tumor cells. TGF-β also is an important regulator of neoangiogenesis. LY2157299 is a small molecule designed to inhibit selectively the serine/threonine kinase of the TGF-β receptor type I (TGF-βRI). Thus, the antitumor effect of LY2157299 is expected to result in an increased tumor immune surveillance, reduced metastatic spread, and decreased tumor-associated neoangiogenesis. The role of TGF-β inhibitors in hepatocellular carcinoma (HCC) was investigated in several in vitro and in vivo studies. TGF-β R1 inhibition by LY2109761 produced several different antitumor activities in HCC preclinical models. The spread of HCC cells in the surrounding tissue is inhibited by the up-regulation of E-cadherin (Fransvea et al. 2008). LY2109761 inhibits invasion of HCC cells (Fransvea et al. 2009) and also inhibits tumor growth thanks to inhibiting neoangiogenesis by reducing vascular endothelial growth factor (VEGF) production (Mazzocca et al. 2009). These effects are selectively dependent on the TGF-1/SMAD-2 pathway (Zhang 2009; Melisi et al. 2008). Finally, LY2109761 inhibits the production of connective tissue growth factor, interrupts the cross talk between tumor and stroma, and blocks the progression of HCC (Mazzocca et al. 2010). Inhibition of TGF-β RI activation using LY364947 inhibits TGF-β-dependent cell signaling and reduces cell motility and invasion in parental and multikinase-resistant HCC cells (Garbay et al. 2010). Given the chemical and biological similarities of LY2109761 and LY364947 with the clinical candidate LY2157299, it is expected that LY2157299 will also have significant antitumor activity in HCC. The present Phase 2 study is a proof of concept to evaluate the quality and quantity of the anti-tumor effect of LY2157299 in patients with HCC.

Clinical Protocol Synopsis: Study H9H-MC-JBAK

Name of Investigational Product: LY2157299	
Title of Study: Phase 2 Study of LY2157299 in Patients with Hepatocellular Carcinoma	
Number of Planned Patients/Subjects: Enrolled/Randomized: approximately 235	**Phase of Development:** Phase 2
Length of Study: 7.5 years Planned first patient visit: Q1 2011 Planned last patient visit: July 2018	

Objectives: The primary objective of this study is to characterize both the time-to-progression (TTP) distributions and the effect on transforming growth factor beta (TGF-β)-associated serum biomarkers (for example, TGF-β, alpha-fetoprotein [AFP], E-cadherin) of study treatment in patients with hepatocellular carcinoma (HCC).

The secondary objectives of the study are:

- To evaluate the safety of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab in HCC patients
- To evaluate the population pharmacokinetics (PK) of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab
- To recommend which doses of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab to use in future trials recruiting HCC patients
- To evaluate the safety and tolerability, pharmacokinetics and efficacy of LY2157299 as monotherapy administered according to a 21 days on/7 days off schedule
- To characterize other time-to-event distributions, such as progression-free survival (PFS, based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 and modified RECIST [mRECIST], for HCC) and overall survival (OS)
- To estimate antitumor efficacy using response rate (RR, based on RECIST 1.1 and mRECIST, for HCC)
- To assess patient-reported outcome (PRO) measures of disease-specific symptoms and health-related quality of life (Functional Assessment of Cancer Therapy Hepatobiliary [FACT-Hep])
- To explore E-cadherin, pSMAD, and β-integrin (and other markers associated with epithelial-to-mesenchymal transition [EMT] transformation and the TGF-β-associated signaling pathway) presence in the original diagnostic tumor tissue and optional posttreatment tumor tissue and the correlation of this with both clinical efficacy endpoints and biomarker response
- To explore the utility of exploratory imaging techniques (for example, positron emission tomography [PET] scan, contrast echography) to assess treatment effect with LY2157299 as monotherapy and in combination with sorafenib when possible
- To explore fibrosis-related biomarkers, such as Fibrotest

Study Design: This is an open-label, multicenter, multicountry, Phase 2 study of LY2157299 in patients with hepatocellular carcinoma. The study design consists of 5 parts. In Part A, patients with AFP ≥1.5x upper limit of normal (ULN) will be randomly assigned to 2 cohorts based on initial dose of LY2157299 to be received (160 or 300 mg/day). In Part B, patients with AFP <1.5x ULN will receive LY2157299 300 mg/day. In Part C, patients with no prior systemic treatment will receive LY2157299 (160 or 300 mg/day) in combination with sorafenib 400 mg twice daily (BID). In Part D, patients with Child-Pugh A liver disease will receive treatment with LY2157299 (160 or 300 mg/day) in combination with ramucirumab (8 mg/kg IV on Days 1 and 15 of each cycle). In Part E, patients with Child-Pugh Class A liver disease and any AFP who have received at least one prior line of systemic therapy or who have not received prior treatment and are ineligible for sorafenib treatment will receive LY2157299 150 mg BID according to a 21 days on/7 days off schedule.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Inclusion Criteria:

[1] Have histological evidence of a diagnosis of HCC not amenable to curative surgery.

[2] Have Child-Pugh Class:

Parts A and B: A or B7
Parts C and D: A
Part E: A

[3] Have serum AFP:

- Part A: ≥1.5x ULN
- Part B: <1.5x ULN

Criterion [3] applies for Parts A and B only.

[4] Have the presence of measurable disease as defined by the RECIST 1.1. A lesion that has been previously treated by local therapy will qualify as a measurable or evaluable lesion if there was demonstrable progression following locoregional therapy.

[5] Age ≥18 years

[6] Have given written informed consent prior to any study-specific procedures

[7] Have adequate organ function including:

- Hematologic: absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥50 x 10^9/L, and hemoglobin ≥8 g/dL.
- Hepatic: bilirubin ≤2.5 times ULN; alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) ≤5 times ULN. Prothrombin time international normalized ratio ≤2.3; or prothrombin time limit is 6 seconds above control.
- Renal: Serum creatinine ≤1.5 times ULN or calculated creatinine clearance >45 mL/min.

Note: Small differences from the outlined laboratory values will be deemed as consistent with the protocol requirements provided that the following criteria are met: they are isolated, are transient, and are not reflective of a medical condition in the opinion of the investigator. Such differences are often a result of biological or laboratory equipment variability. To confirm that these results are within biological or laboratory equipment variability, repeat laboratory/hematological tests should be done prior to dosing the patient on Cycle 1 Day 1.

[8] Have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale.

[9] Have:

In Parts A and B:
- received sorafenib and have progressed or were intolerant to sorafenib, or
- are ineligible for sorafenib treatment (at the investigator's discretion).

In Part C: not received previous systemic treatment.

In Part D:
- received sorafenib and have progressed or were intolerant to sorafenib, or
- are ineligible for sorafenib treatment (at the investigator's discretion), or
- have not received prior systemic treatment (at the investigator's discretion).

In Part E:
- received at least one prior line of systemic therapy, or
- not received prior treatment and are ineligible for sorafenib treatment (at the investigator's discretion).

[10] In Parts A, B, D and E: have discontinued sorafenib for at least 2 weeks.

Exclusion Criteria:

[15] Are currently enrolled in, or discontinued within the last 28 days from a clinical trial involving an investigational drug or device or not approved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[16] Known HCC with fibro-lamellar or mixed histology.

[17] Presence of clinically relevant ascites.

[18] Liver transplant requiring increased immunosuppressive therapy. (Patients on maintenance immunosuppressive therapy after liver transplant are eligible for Parts A and B. Rapamycin analogues are not allowed.)
[19] Have received >1 line of systemic treatment in Parts A, B, and D.
[20] Have moderate or severe cardiac disease.

[21] Have serious preexisting medical conditions that, in the opinion of the investigator, cannot be adequately controlled with appropriate therapy or would preclude participation in this study.
[22] Females who are pregnant or lactating.
[23] Have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix) unless in complete remission and off all therapy for that disease for a minimum of 3 years.
At the discretion of the investigator, hormone-refractory prostate cancer patients who are stable on gonadotropin-releasing hormone (GnRH) agonist therapy and breast cancer patients who are stable on antiestrogen therapy (for example, an aromatase inhibitor) may have that treatment continued while they are enrolled in this study.
[24] Have active infection that would interfere with the study objectives or influence study compliance.
[25] For Part C, have a known hypersensitivity to sorafenib or its excipients.
[26] For Part D, have a serious illness or medical condition(s), including but not limited to the following:

a) The patient has undergone major surgery within 28 days prior to randomization or has undergone central venous access device placement within 7 days prior to randomization.
b) The patient has uncontrolled arterial hypertension ≥150 / ≥90 mm Hg despite standard medical management.
c) The patient is receiving ongoing therapy with nonsteroidal anti-inflammatory agents (NSAIDs) (eg, indomethacin, ibuprofen, naproxen, nimesulide, celecoxib, etoricoxib, or similar agents) or other antiplatelet agents (eg, clopidogrel, ticlopidine, prasugrel, dipyridamole, picotamide, indobufen, anagrelide, triflusal, or similar agents). Aspirin at dosages up to 100 mg/day is permitted.
d) The patient is receiving therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents. Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that the coagulation parameters defined in the inclusion criteria are met.
e) Uncontrolled thrombosis (including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within 6 months prior to randomization) or bleeding.
f) The patient has experienced any Grade 3 or 4 gastrointestinal bleeding or any variceal bleeding episode in the 3 months prior to randomization requiring transfusion, endoscopic or operative intervention (patients with any bleeding episode considered life-threatening during the 3 months prior to randomization are excluded, regardless of transfusion or intervention status). Patients who have esophageal or gastric varices that require immediate intervention or represent a high bleeding risk in the opinion of the investigator or consulting gastroenterologist or hepatologist are excluded.
g) Elective or planned major surgery to be performed during the course of the clinical trial.
h) Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to randomization.
i) Known allergy or hypersensitivity to monoclonal antibody treatment or any components used in the ramucirumab drug product preparation.
j) The patient's urinary protein is >1+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates ≥2+ proteinuria, then a 24-hour urine must be collected and must demonstrate <1000 mg of protein in 24 hours to allow participation in the study.
k) The patient has either a history of or current hepatic encephalopathy or current clinically meaningful ascites. *Clinically meaningful ascites* is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

Test Product, Dosage, and Mode of Administration: Parts A and B: LY2157299 is administered orally by daily dosing morning and evening (BID) at either 80 or 150 mg per dose (total dosage of 160 or 300 mg daily) for 14 days, followed by 14 days with no study drug. (The exception is for patients who will have a Day 15 PK sample taken, who will omit the evening dose on Day 14.) This on/off schedule constitutes a cycle of 28 days. In extenuating circumstances, the "on study drug" window is allowable from Day 10 to Day 14. Part C: LY2157299 is administered orally by daily dosing morning and evening (BID) at either 80 or 150 mg per dose (total dosage of 160 or 300 mg daily) for 14 days, followed by 14 days with no study drug. Sorafenib is administered orally by daily dosing morning and evening (BID) at 400 mg per dose (total dosage of 800 mg daily) for 28 days. This constitutes a cycle of 28 days. Part D: LY2157299 is administered orally by daily dosing morning and evening (BID) at either 80 or 150 mg per dose (total dosage of 160 or 300 mg daily) for 14 days, followed by 14 days with no study drug. Ramucirumab is administered intravenously at 8 mg/kg on Days 1 and 15 of every cycle. This constitutes a cycle of 28 days. Part E: LY2157299 is administered orally by daily dosing morning and evening (BID) at 150 mg per dose (total dosage of 300 mg daily) for 21 days, followed by 7 days with no study drug.
Planned Duration of Treatment Per Patient: Per patient, the screening period is no more than 4 weeks or 28 days before the first dose of LY2157299; the planned treatment duration is 6 cycles or approximately 24 weeks. However, patients may receive LY2157299 until their disease has progressed, the patient has died, or the patient discontinues for adverse events, investigator's judgment, or other reasons. Wash-out period: none. **Planned Follow-Up Observation Period Per Patient:** Follow-up visits consist of a visit approximately 30 days after the last study treatment and any subsequent follow-up approximately every 60 days (approximately 2 months) (±7 days). Patients who have discontinued study treatment without progression will continue to be followed for progression. Every attempt should be made to gather all information every 2 months (radiological scans and survival), even if a patient starts a new anticancer therapy. All patients will be followed until death. Patients who have entered the treatment extension period will be followed for just 30 days after treatment discontinuation.
Reference Therapy, Dose and Mode of Administration: Not applicable
Criteria for Evaluation: Efficacy: RECIST 1.1 and mRECIST, (mRECIST for HCC) for RR, TTP and PFS Safety: International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 Health Outcomes: PRO measures of disease-specific symptoms and health-related quality of life (FACT-Hep) Bioanalytical: Plasma LY2157299/sorafenib/ramucirumab concentrations will be analyzed by liquid chromatography/mass spectrometry/mass spectrometry

Statistical Methods:

Outline of Design: Approximately 235 Child-Pugh Class A or B7 patients with HCC will be enrolled into this study. In Parts A and B, patients were initially randomly assigned onto 1 of 2 doses, balanced based on AFP levels (≤400 ng/mL and >400 ng/mL), etiology, and whether sorafenib-naïve or not. A planned interim analysis after approximately 10 (for PK and acute safety) patients enrolled into each dose and completed 1 cycle was carried out. The second interim analysis for futility of 1 or both doses was not carried out but, as part of the continuous monitoring of safety, PK, and laboratory markers in patients with HCC, the sponsor noted that patients in both cohorts were staying on study beyond 4 months. An additional data review was carried out based on 64 enrolled patients, and a decision was made to stop enrollment to the 160 mg/day dose and continue enrollment to the 300 mg/day dose until 70 patients were treated. The protocol was amended (Amendment [b]) to have 3 parts. The 2 cohorts planned in the original protocol and in Amendment (a) were designated as Part A. Part B enrolled approximately 40 patients with AFP levels <1.5x ULN and treated them with 300 mg/day intermittent dosing. Two interim analyses were planned for Part B – one after the last of 70 patients with elevated AFP levels in Cohort 2 started Cycle 1, and the second after 18 patients enrolled into Part B and were actively followed for at least 3 months or discontinued from study treatment. Part C enrolled approximately 47 Child-Pugh Class A patients and consisted of a safety lead-in of 2 dose-escalation cohorts followed by an expansion cohort where the selected dose(s) of the combination treatment were evaluated. Part D will enroll approximately 18 Child-Pugh Class A patients into 2 dose-escalation cohorts. Part E will initially enroll up to approximately 23 patients. This would give a total of approximately 235 patients enrolled.

Safety: Summary statistics, plots, and listings for all safety data collected will be provided in aggregate and by dose in Part A and Part C, and in aggregate for Part B separately. Comparisons between doses and parts will be summarized for Part A and Part B, and may be compared to Part C. Data from Part D and Part E will be summarized separately from the data in Parts A, B, and C.

Clinical Efficacy: Time-to-event distributions will be characterized for each dose in each part (where data allow) using Kaplan-Meier methods, and various time-to-event parameters, such as median TTP, PFS, and OS and their rates at specified time points, will be estimated from their respective distributions. The hazard ratios between doses for patients with elevated AFP levels and between groups of patients with elevated AFP and AFP levels <1.5x ULN at 300 mg/day will be estimated. Sensitivity analyses using alternative models may also be performed. RR will be summarized by dose and part. Stratification factors used in the randomization of Part A may be included as covariates in analyses between doses. Beginning with Amendment (b), patients will no longer be randomized onto treatment, but the same covariates may be considered in analyses of clinical endpoints. Data from Part D and Part E will be summarized separately from the data in Parts A, B, and C.

Health Outcomes: Summary descriptive statistics by study part will be provided for the PRO data (FACT-Hep) at each time point and change from baseline. Time to worsening of symptoms will also be evaluated.
Pharmacokinetics: A population PK analysis will be performed on all patients receiving LY2157299. A PK analysis will be performed for sorafenib as well for some patients enrolled in Part C. This analysis will explore the impact of covariates such as demographic factors and markers on the relevant PK parameters. In Part D, the LY2157299 and ramucirumab PK administered in combination will be characterized. In Part E, the PK of LY2157299, when administered according to a 21 days on /7 days off treatment schedule, will be characterized.
Pharmacodynamics: Changes in response biomarkers, such as pSMAD in tumor tissue (or other TGF-β-related biomarkers) and lactate dehydrogenase, AFP, E-cadherin in serum will be estimated and may be correlated with clinical efficacy. Exploratory population PK/pharmacodynamic analyses may be conducted to identify the exposure-biomarker response relationship.

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4. Abbreviations and Definitions

Term	Definition
adverse event (AE)	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.
ADME	absorption, distribution, metabolism, excretion
AFP	alpha-fetoprotein
ALT	alanine aminotransaminase
ANC	absolute neutrophil count
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
AST	aspartate aminotransaminase
AUC(0-∞)	area under the concentration-time curve, zero to infinity
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).
BID	twice a day
BNP	brain natriuretic peptide
blinding/masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor(s), and in some cases, select sponsor personnel being unaware of the treatment assignment(s).
CART	classification and regression tree
case report form (CRF) and electronic case report form (eCRF)	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.
CI	confidence interval
CL	clearance

clinical research physician (CRP)	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.
CL_{ss}/F	apparent clearance at steady state
$C_{max,ss}$	maximum observed drug concentration at steady state
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.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial.
CR	complete response
CrCL	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	ejection fraction
EIAED	enzyme-inducing anti-epileptic drug
EMT	epithelial-to-mesenchymal transition
end of study (trial)	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study. The European Union has additional reporting requirements associated with the end of study. Consult regional SOPs for further information.

EU	European Union
F344	Fischer 344
FACT-Hep	Functional Assessment of Cancer Therapy, Hepatobiliary
FACIT	Functional Assessment of Chronic Illness Therapy
FFPE	formalin-fixed paraffin-embedded
FHD	first-into-human dose
FHSI-8	Focal High Signal Intensity 8
GBM	glioblastoma multiforme
GCP	good clinical practice
GLP	good laboratory practice
GnRH	gonadotropin-releasing hormone
HCC	hepatocellular carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug
INR	International Normalized Ratio
institutional review board/ethical review board (IRB/ERB)	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
intention to treat (ITT)	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.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
K_i	inhibition constant
LD	longest diameter
LA	left atrial
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 trial.
LV	left ventricular
LVEF	left ventricular ejection fraction
MAP	multi-analyte panel
MOS	margin of safety
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable
NOEL	no observed effect level
NONMEM	nonlinear mixed-effect modeling
NSAID	nonsteroidal anti-inflammatory drug
ORR	overall response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic or progressive disease
per protocol set	The set of data generated by the subset of patients who sufficiently complied

(PPS)	with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PR	partial response
PRF	pulse repetition frequency
PRO	patient-reported outcome
PS	performance status
PSA	prostate-specific antigen
PT	prothrombin time
RA	accumulation ratio
randomize	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.
RECIST, mRECIST	Response Evaluation Criteria in Solid Tumors, modified RECIST
RR	response rate
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 trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SD	stable disease
SLD	sum of the longest diameter
SOP	standard operating procedure
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
$t_{1/2}$	half life

TGF-β	transforming growth factor beta
TGF-β RI	transforming growth factor beta receptor type I
$t_{max,ss}$	time to maximum concentration at steady state
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment (also called treatment-emergent signs and symptoms [TESS]).
TTP	time-to-tumor progression
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at steady state
WHO	World Health Organization

Phase 2 Study of LY2157299 in Patients with Hepatocellular Carcinoma

5. Introduction

Hepatocellular carcinoma (HCC) represents the sixth most common cancer worldwide with a still increasing incidence (Parkin et al. 2005). Patients with chronic liver disease and cirrhosis are at high risk for HCC; thus the prognosis, which is usually poor, is related to underlying liver function in addition to disease stage.

Patients with HCC considered to have noncurable disease include those for whom liver transplant, resection, tumor embolization, or other percutaneous ablation are not suitable. For these patients, the median survival time with no treatment ranges from 40 months for patients with multinodular asymptomatic tumors to about 5 months for those with cancer-related symptoms, vascular disease, or extrahepatic spread. For this patient population, tumor chemoembolization and recently sorafenib are the only options with survival impact. In the recently presented SHARP trial (Phase 3), which compared sorafenib with placebo in patients with advanced liver cancer with no prior systemic treatment, performance status (PS) 0 to 2, and a Child-Pugh status A, the hazard ratio (HR) for overall survival (OS) was 0.69 (95% confidence interval [CI]: 0.55, 0.87; p=.0006) in favor of sorafenib, representing a 44% improvement in OS compared with placebo. The median OS was 10.7 and 7.9 months with an HR for time-to-tumor progression (TTP) of 0.58 (95% CI: 0.45, 0.74; p=.000007). The median TTP was longer (5.5 versus 2.8 months) with sorafenib than with placebo (Llovet et al. 2008). Given these results, sorafenib is the first-line standard of care for patients with advanced liver cancer who are not candidates for surgical or local treatment. However, if the treatment with sorafenib failed, there is no approved second-line therapy. In patients with Child-Pugh B status, the benefit of sorafenib treatment over best supportive care is not proven. TTP after sorafenib treatment in patients with moderate to advanced cirrhosis is estimated to be 2.8 months (Pinter et al. 2009).

Different agents have been tested as second-line therapy in HCC patients (Table JBAK.1). Time to progression without any treatment is estimated to be 2.7 months (Llovet et al. 2012).

Table JBAK.1. Examples of Experimental Treatments as Second-Line Therapy in Patients with Hepatocellular Carcinoma

Study	Patient (n)	Treatment	Time to Progression or Time to Treatment Failure (median months)	Method	Response Rate	OS (median, months)	Reference
Phase II	46	Brivanib	2.7	mWHO (assessed by PI)	4.3%	9.7	Finn et al. 2012
			1.77 (95% CI, 1.38–4.01)	mWHO (assessed by IRRC)	4.3%		
			6.9 (95% CI, 3.9–NR)	mRECIST (assessed by independent radiologist)	10.9%		
Phase III	263	Brivanib	4.2	mRECIST	11.5%	9.4	Llovet et al. 2012
	132	Placebo	2.7	mRECIST	1.9%	8.2	
Phase I/II	28	Everolimus	3.9 (95% CI, 2.1-5.5)	RECIST	4%	8.4	Zhu et al. 2011
Phase II	38	Sunitinib	2.9 (95% CI, 0.5-15)	-	6%		Yau et al. 2011
Phase II	11	Sunitinib	3.2	RECIST		8.4	Wörns et al. 2010
Phase II	18	Gemcitabine Oxaliplatin	PFS 3.2 (95 % CI, 2.3–3.9)			4.7	Mir et al. 2012
Phase III	283	Ramucirumab	3.48	RECIST	7.1%	9.17	Zhu et al. 2015
Phase III	573	Regorafenib	3.2	mRECIST	10.6%	10.6	Bruix et al. 2016

Abbreviations: CI = confidence interval; IRRC= independent response review committee; mRECIST = modified Response Evaluation Criterial in Solid Tumors; mWHO = modified World Health Organization; NR = not reached; OS = overall survival; PFS = progression free survival; PI – principal investigator.

Transforming growth factor beta (TGF-β) has been shown to be a tumor promoter in advanced, metastatic cancer, while in normal tissue, TGF-β inhibits epithelial cell proliferation (de Caestecker et al. 2000; Massagué et al. 2000; Derynck et al. 2001; Wakefield and Roberts 2002). Because of this tumor-promoting activity, TGF-β inhibition is currently being considered as a treatment option in patients with advanced cancer (Yingling et al. 2004).

TGF-β signals into the cell by engaging TGF-β Type I and Type II receptors and inducing phosphorylation of the TGF-β receptor kinases (Shi and Massagué 2003). The Type I receptor kinase phosphorylates SMAD2 and SMAD3 resulting in the formation of SMAD complexes, which are subsequently translocated into the nucleus to stimulate gene transcription of TGF-β responsive genes (Derynck et al. 2001). Therefore, assessment of phosphorylated SMAD (pSMAD) after TGF-β activation can be used to determine the ability of the host to respond to TGF-β activation.

Several mechanisms have been proposed to explain the tumor-promoting activity of TGF-β such as increased neovascularization of the tumor causing increased nourishment to the tumor cells, immunosuppression leading to the escape of tumor immune surveillance, and increased migration and invasion resulting in metastasis (Akhurst and Derynck 2001; Derynck et al. 2001; Siegel and Massagué 2003). These combined effects on the tumor microenvironment by TGF-β promote tumor progression, and therefore a TGF-β receptor type I (TGF-β RI) kinase inhibitor is expected to cause arrest of tumor growth and metastasis in patients.

It has been reported that TGF-β1 is increased in HCC patients and correlates with worst prognosis. In addition, plasma TGF-β1 levels are elevated in HCC patients with alpha-fetoprotein (AFP) levels above 10 IU/mL (Sacco et al. 2000).

TGF-β is a pro-fibrotic cytokine and induces HCC progression through a paracrine mechanism, which is abrogated by inhibition of TGF-β/SMAD signaling in hepatocytes (Gressner et al. 2002; Mikula et al. 2006). HCC progression is also frequently associated with an epithelial-to-mesenchymal transition (EMT) of hepatocytes that may be caused by the cooperation of laminin 5 and TGF-β (Giannelli et al. 2005). TGF-β stimulation induces EMT and invasion in HCC while its inhibition is association with decrease of invasion (van Zijl 2009)

A recent review integrating the gene expression data from 9 different human genetic expression studies across various geographies and stages of HCC was able to propose 3 distinct genetic patterns associated with disease outcome (Hoshida et al. 2009). In this genetic expression assessment, the β-catenin and TGF-β-induced gene expression was associated with poor survival. AFP was found to differentiate between the proposed 3 clusters (S1 to S3).

Although the clinical candidate LY2157299 has not yet been investigated in HCC models, surrogate compounds, such as LY2109761, have been used to elucidate the antitumor effect of the TGF-β inhibition in several in vitro and in vivo studies. TGF-β R1 inhibition by LY2109761 produced several different antitumor activities in HCC preclinical models. The spread of HCC cells in the surrounding tissue is inhibited by the up-regulation of E-cadherin (Fransvea et al. 2008). LY2109761 inhibits invasion of HCC cells (Fransvea et al. 2009) and also inhibits tumor growth thanks to inhibiting neoangiogenesis by reducing vascular endothelial growth factor

(VEGF) production (Mozzacca 2009). These effects are selectively dependent on the TGF-1/SMAD-2 pathway (Zhang 2009; Melisi et al. 2008). Finally, LY2109761 inhibits the production of connective tissue growth factor, interrupts the cross-talk between tumor and stroma, and blocks the progression of HCC (Mazzocca et al. 2010). Inhibition of TGF-β RI activation using another surrogate compound, LY364947, also inhibits TGF-β-dependent cell signaling and reduces cell motility and invasion in parental and multikinase-resistant HCC cells (Garbay et al. 2010).

These data support the study of TGF-β inhibitors in HCC. LY2157299 is a small molecule designed to inhibit selectively the serine/threonine kinase of the TGF-β RI. Thus, the antitumor effect of LY2157299 is expected to result in an increased tumor immune surveillance, reduced metastatic spread, and decreased tumor-associated neoangiogenesis.

5.1. LY2157299 – Nonclinical and Clinical Experience

5.1.1. Nonclinical Pharmacokinetics of LY2157299

Nonclinical pharmacokinetic (PK) studies were performed in 2 species, rat and dog. LY2157299 exposure was examined in rats following daily oral doses of 15, 50, and 150 mg/kg after 1 dose and 28 doses. The PK of LY2157299 were linear, but female rats had a consistently higher (approximately 2-fold) exposure over the course of the study. LY2157299 is rapidly absorbed and eliminated with a half-life ($t_{1/2}$) of approximately 4 to 8 hours.

As determined by metabolism studies in rats, most of LY2157299 was excreted in feces. Three metabolites have thus far been identified. The function and activity of these metabolites have not been defined at this time.

In the nonrodent studies using dogs, a gastric pH-dependent variability was observed suggesting that at acidic pH, LY2157299 had a less variable exposure. To reduce possible PK variability, LY2157299 will be administered on an empty stomach.

Male and female Fischer 344 (F344) rats were given daily oral doses of LY2157299 monohydrate at 0, 15, 50, or 150 mg/kg for 1 month. Male and female beagle dogs were given daily oral doses of LY2157299 monohydrate at 0, 50, 250, or 500 mg/kg for 1 month. The potential for induction of hepatic microsomal drug-metabolizing enzymes was evaluated by quantitating total cytochrome P450 (CYP) content in liver samples collected at necropsies. Slight but variable changes in total CYP content were observed in treated male rats, while no significant changes were observed in treated female rats. No statistically significant changes in total CYP content were observed in treated beagle dogs. The magnitude of the changes observed in male rats and the lack of significant change in female rats and male and female dogs suggest that LY2157299 is not an inducer of overall CYP content under the conditions of these studies.

The ability of LY2157299 to inhibit CYP-mediated metabolism in vitro was examined. The data show that LY2157299 would not be expected to inhibit metabolism mediated by CYP2D6, CYP2C19, CYP2C9, and CYP1A2. LY2157299 was found to competitively inhibit the biotransformation of midazolam to 1'-hydroxymidazolam, a marker activity for CYP3A4,

yielding an inhibition constant (K_i) value of 44 μM. LY2157299 was found to competitively inhibit the biotransformation of testosterone to 6β-hydroxytestosterone, a marker activity for CYP3A4, yielding a K_i value of 290 μM.

Based on the nonclinical metabolism studies, LY2157299 is not anticipated to have the potential to accumulate in patients or have a risk of high hepatic metabolism.

For details on the nonclinical PK of LY2157299, please see the Investigator's Brochure (IB).

5.1.2. Nonclinical Pharmacokinetic/Pharmacodynamic Model

Because regular assessment of pSMAD in tumor tissue in patients is both too invasive and likely to produce variable results given the heterogeneous nature of tumor tissue, a specific bioassay was developed to determine pSMAD levels in a surrogate tissue, peripheral blood mononuclear cells (PBMC) (data on file, Eli Lilly; Farrington et al. 2007). To compare the effect of LY2157299 between the surrogate and tumor tissue, the pSMAD level changes measured in both PBMC and 4T1 tumor tissue in rats treated with LY2157299 was investigated. A significant relationship between pSMAD modulation in tumor cells and in peripheral blood was observed at 30- and 300-mg/kg doses (p-values were 0.002 and 0.059 in the 30- and 300-mg/kg groups, respectively, and <.0001 for the combined data) which suggests that the pSMAD modulation in human PBMC should be a useful surrogate of the pharmacodynamic (PD) effect of LY2157299.

A PK/PD model was developed to characterize the relationship between drug concentrations and pSMAD levels. This PK/PD model integrated the time course of the PK of the compound, the inhibition of pSMAD in tumor and PBMC, as well as the nonclinical tumor growth delay of 3 tumor animal models. This model was used to predict an anticipated dose range that is likely to be biologically effective in patients with cancer. The simulations from the rat and the mouse suggest that a range of 200 to 500 mg (total daily doses), administered twice daily are expected to produce the required percentage inhibition of pSMAD that has been associated with tumor-growth delay in the preclinical studies.

For details refer to the IB.

5.1.3. Clinical Pharmacokinetics of LY2157299

As of 19 August 2011, 39 patients have been treated with LY2157299 in an ongoing study, Study H9H-MC-JBAH (JBAH). Of 39 patients, noncompartmental PK analysis has been performed on 37 patients.

Results from all 5 cohorts showed rapid absorption of LY2157299, as demonstrated by measurable plasma concentrations at the first sampling time (0.5 to 2 hours). At steady state, on Day 14, the median time to maximum concentration ($t_{max,ss}$) ranged from 0.5 to 2 hours postdose, independent of dose. Both the maximum observed concentration at steady state ($C_{max,ss}$) and exposure increased with dose. The geometric mean of the apparent clearance at steady state (CL_{ss}/F) was similar across Cohorts 3, 4, and 5, whereas for the first 2 cohorts the scheduled sampling time was only up to 8 hours post dose and the parameter could not be estimated with any degree of certainty. No accumulation of LY2157299 in the 5 cohorts was

observed over the 14-day twice-daily (BID) dosing regimen, with accumulation ratio (RA) observed to be approximately 1. A population PK model, based on Cohorts 1 through 5 data, was developed. A first order absorption linear 2-compartment model, with elimination from the central compartment provided the best fit to the plasma data. The mean population clearance of LY2157299 was 38.4 L/h with standard error, expressed as a percentage coefficient of variation of 8% and the steady state volume of distribution (V_{ss}) was 193 L. From the population PK analysis of all 5 cohorts' data, the between-patient variance was estimated to be 46% on the population apparent clearance. The between-occasion variability on apparent CL was estimated at 18%.

The dose-proportionality analysis was performed for the PK parameters area under the plasma concentration-time curve from 0 to infinity (AUC[0-∞]) and $C_{max,ss}$ (Day 15) using results from 30 patients from all 5 cohorts (pooled across Cycles 1 and 2 for Cohorts 3, 4, and 5). From this analysis, there was no evidence of a difference between Cycles 1 and 2 for Cohorts 3, 4, and 5. The estimated ratios of geometric means for AUC(0-∞) and $C_{max,ss}$ between 150 mg BID and 20 mg BID were estimated as 7.90 (90% CI: 2.85, 22.0) and 3.56 (90% CI: 2.09, 6.06), respectively. For a doubling of dose, the fold increases for AUC(0-∞) and $C_{max,ss}$ are 2.04-fold with corresponding 90% confidence limits (1.43, 2.89) and 1.55-fold with 90% confidence limits (1.29, 1.86), respectively. Within- and between-patient coefficients of variation were estimated as 26% and 40% for AUC(0-∞) at steady state, respectively, and 34% and 56% for $C_{max,ss}$, pooled across the 5 cohorts from the dose-proportionality analysis.

For additional information see Section 6.1 in the IB.

5.1.4. Nonclinical Toxicology of LY2157299

The toxicity of LY2157299 has been characterized in repeat- and intermittent-dose nonclinical safety studies up to 6 months duration in the rat and dog. The following paragraphs summarize the major findings in rats and dogs.

The heart and great vessels are major target organs for toxicity in both F344 rats and beagle dogs following treatment with LY2157299. These effects include valvulopathy and vascular lesions of multiple blood vessels at the base of the heart in rat and dog, which in the rat appear to be partially reversible. In the rat, a continuum of changes in the gastrointestinal tract have been described, including inflammation of the mucosa, simple mucosal hyperplasia, and adenocarcinoma following 6 months of continuous treatment. Based on safety pharmacology studies, administration of LY2157299 produced increases in hexobarbital-induced sleep time. Administration of LY2157299 may produce dose-dependent hemodynamic side effects, measured by decreased blood pressure and increases in heart rate, which can be easily monitored in the clinic and are reversible upon cessation of treatment. The nonclinical data do not reveal any substantive clinical risk of QT/QTc prolongation at doses that result in total plasma concentrations of at least 3.3 μg/mL.

LY2157299 was negative in a bacterial mutation test (Ames test) and an in vivo mammalian test (mouse micronucleus). However, LY2157299 was positive in an in vitro mammalian test

(chromosome aberration) with and without S9 activation. This positive finding is considered acceptable in the intended patient population.

Rats were dosed up to 3 months intermittently or 6 months continuously at 50, 150, and 250 mg/kg. Dogs have been dosed with up to 500 mg/kg for 1 month and 8, 20, and 60 mg/kg daily for 6 months. LY2157299 caused mortality in the rat at progressively lower doses as the duration of treatment increased. In shorter-duration studies, mortality was observed in rats administered 1200 mg/kg of LY2157299 in a 14-day pilot study and in the 3- and 6-month rat studies, mortality occurred in animals receiving daily doses of 150 (6-month study) and 250 mg/kg (3- and 6-month study) beginning on Days 83 and 54, respectively. All preterminal deaths in rats were attributed to compound-related inflammation of the aorta and distributing arteries at or near the base of the heart, except for 1 male for which the cause of death was undetermined and 1 male that died of an intestinal adenocarcinoma (6-month study). One female dog in the high-dose reversibility group (500 mg/kg) died shortly after the treatment phase ended in the 1-month study; death was attributed to bile peritonitis. There was no mortality observed in the 6-month dog study. Vascular lesions in the rat were characterized by minimal-to-severe inflammation of multiple blood vessels at the base of the heart including the ascending aorta, coronary arteries, and distributing arteries of the aortic arch. These changes were described in the 3-month (150 and 250 mg/kg) and 6-month (≥50 mg/kg) continuous-dose groups. The vascular damage in rats administered ≥150 mg/kg continuously for 3 and 6 months and 2 weeks on/2 weeks off correlated with serum chemistry and hematologic responses typical of chronic hemorrhage and inflammation. In rats given 150 and 250 mg/kg (mid and high dose, 6 months and ≥3 months, respectively), vascular inflammation was, in some animals, associated with vascular rupture resulting in acute hemorrhage into the thoracic cavity and death.

The no-observed-effect level (NOEL) for vascular damage in the rat is 50 mg/kg administered on a 2-weeks-on/2-weeks-off schedule. Changes in the base of the ascending aorta, characterized by minimal-to-marked degeneration, disorganization, and separation of intramural elastic laminae without an accompanying inflammatory response, were observed in the dog administered daily doses of 8, 20, or 60 mg/kg for 6 months. The aortic mural degeneration was focally extensive or multifocal with no compound-related microscopic changes in the descending aorta. Although the microscopic changes likely compromised regional aortic structural integrity, there were no diagnostic changes of an aortic aneurysm – no gross dilation, no effects in the intimal layer, and a lack of free blood within the wall of the aorta. A cardiac valvulopathy, characterized by endothelial/stromal cell proliferation, inflammation, and increases in smooth muscle actin immunolabeling and hemorrhage was identified in rats and dogs given high doses of LY2157299 for ≤30 days. In the 3- and 6-month studies, compound-related valvulopathy of similar character occurred at lower doses than previously described in studies ≤30 days in duration (150 and 250 mg/kg [intermittent 2 weeks on/2 weeks off and continuous groups] in the 3-month study and at all doses [50, 150, and 250 mg/kg] in the rat 6-month study and at the mid and high doses [20 and 60 mg/kg] in the dog). The cardiac valvulopathy observed in rats and dogs given LY2157299 were observed but have not been associated with extracardiac evidence of valvular insufficiency or dysfunction. The NOEL for valvulopathy in the rat is 50 mg/kg administered on a 2-weeks-on/2-weeks-off schedule and 8 mg/kg in the dog in the 6-month

study. In an effort to characterize the reversibility of cardiovascular lesions, a non-good laboratory practice (GLP) study in rats administered 250 mg/kg daily for 8 weeks followed by a 6-week recovery period was conducted. Data indicate that vascular lesions are partially reversible when rats are administered a dose known to induce a high incidence of cardiovascular lesions (vasculitis and valvulopathy) with daily dosing. After the 6-week recovery period, a decrease in both incidences in severity of cardiovascular lesions was observed. However, at the end of this recovery period, a few animals still were observed with minimal-to-moderate inflammation at the base of the aorta, coronary arteries or valves, and minimal stromal hyperplasia of the atrioventricular valves. These lesions were still considered adverse.

Treatment with LY2157299 results in a continuum of changes characterized by inflammation in the mucosa of mid- and high-dose (150 and 250 mg/kg) rats dosed either daily or intermittently for 3 months to proliferative changes at the mid and high dose (150 and 250 mg/kg) in the 6-month daily-dosing rat study. The proliferative changes included simple mucosal hyperplasia that progressed to include adenomatous hyperplasia, adenoma, and, in 2 males at the high dose, adenocarcinoma.

In the rat, additional important compound-related findings affecting the skeletal system, consisting of proliferation of trabecular bone or sternal cartilage, altered endochondral ossification, and slightly increased degeneration of articular cartilage were observed. Consistent with literature predictions (Lahn et al. 2005), administration of LY2157299 in a pilot embryo-fetal study resulted in increased resorptions and fetal skeletal morphology at 20 and 200 mg/kg. A no effect level for embryo-fetal effects was established at 2 mg/kg in this pilot study. In the dog, corneal edema and episcleritis were noted in the eyes of dogs at the high dose (60 mg/kg) during a scheduled ophthalmologic examination of all dogs on Day 176. Corneal endothelitis (inflammation of the most posterior cell layer of the cornea) was considered to be the primary change. Histologic evaluation of the eye was unremarkable. Additional important compound-related findings in the dog consisted of atrophy and/or inflammation of the mucosa of the stomach and large intestine, proliferation of sterna cartilage, and gallbladder mucification.

For additional information, see Section 5 in the IB.

5.1.4.1. Overall Conclusions

Collectively, the findings in the continuous 3- and 6-month daily-dosing toxicity studies, particularly the degeneration of the large blood vessels, imply that long-term, daily dosing of LY2157299 may carry a risk in patients for developing aneurysms. Reversibility was not assessed in the 3- or 6-month toxicity studies, but in a non-GLP reversibility study in rat, data indicate the cardiovascular lesions are partially reversible, but those that are still present following the recovery period are still adverse. The intermittent-dosing regimen in patients is based on the safety demonstrated in the rat and dog following 1 month of continuous daily dosing in which the NOEL for any effects in the heart was 150 and 20 mg/kg in the rat and dog, respectively, and a 3-month intermittent-dosing study in the rat in which the NOEL for any effects in the heart was 50 mg/kg (see Table JBAK.2 for margin-of-safety [MOS] calculations). Although the likelihood of occurrence or the extent and timing of such a risk observed after daily

dosing is not known in humans, LY2157299 will be administered as an intermittent-dosing regimen in this patient population which has a poor prognosis and rapidly advancing cancer.

Table JBAK.2. Margin of Safety Based on NOEL to Cardiovascular Effects

Clinical Dose (mg/day)			**160**	**300**
Measured $AUC_{0\text{-}24hr}$ (μg•hr/mL) at steady state BID			2.2	4.3
Simulated $AUC_{0\text{-}24\ hr}$ (μg•hr/mL) at steady state QD[a]			4.1	7.7
Rat NOEL[b] (150 mg/kg) (30 days; daily dosing)				
$AUC_{0\text{-}24\ h}$ (μg•hr/mL)[c]	36.3	Measured (Steady State BID)	16.5	8.4
		Simulated[a] (Steady State QD)	8.9	4.7
Rat NOEL[b] (50 mg/kg) (3-months intermittent; 2 weeks on/2 weeks off)				
$AUC_{0\text{-}24\ h}$ (μg•hr/mL)[c]	8.0	Measured (Steady State BID)	3.6	**1.9**
		Simulated[a] (Steady State QD)	2.0	1.0
Rat LOEL (150 mg/kg) (3-months intermittent; 2 weeks on/2 weeks off)				
$AUC_{0\text{-}24\ h}$ (μg•hr/mL)[c]	24.2	Measured (Steady State BID)	11	5.6
		Simulated[a] (Steady State QD)	5.9	3.1
Dog NOEL[b] (20 mg/kg) (30 days; daily dosing)				
$AUC_{0\text{-}24\ h}$ (μg•hr/mL)[d]	23.9	Measured (Steady State BID)	10.9	5.6
		Simulated[a] (Steady State QD)	5.8	3.1

Margin of safety based on NOEL to cardiovascular effects in 30 day daily and 3-month intermittent dosing GLP toxicology studies in rat and dog and measured clinical AUC (shaded row indicates the relevant MOS for LY2157299) or exposure multiple to an effect dose (LOEL) for cardiac lesions in the rat in a 3-month intermittent dosing GLP toxicology study.

Abbreviations: AUC = area under the concentration curve; BID = twice daily; GLP = good laboratory practice; LOEL = lowest-observed-effect level; MOS = margin of safety; NOEL = no-observed-effect level; QD = daily.

[a] Simulations based on all clinical data from Study JBAH (Cohorts 1 to 5) assuming QD dosing.

[b] NOEL is based on absence of any cardiovascular changes at this dose.

[c] AUC from males were used to calculate MOS or exposure multiple to the LOEL.

[d] AUC from males and females was averaged since no exposure differences were noted.

5.1.5. Clinical Experience

5.1.5.1. Safety

As of 15 September 2015, approximately 696 patients and 20 healthy subjects have received treatment with LY2157299, either in monotherapy or in combination with chemotherapy. These include clinical trial patients with advanced/metastatic cancer, solid tumors, glioblastoma, pancreatic cancer, HCC and myelodysplastic syndromes (MDS).

Overall, few SAEs deemed by investigators to be associated with drug treatment have been reported. Most treatment-related SAEs have been reported in 1 patient except anemia (2 patients

with HCC), cardiac failure (2 patients with MDS), neutropenia (1 patient with glioblastoma and 1 patient with HCC), thrombocytopenia (2 patients with glioblastoma), peritoneal hemorrhage (2 patients with HCC), and diarrhea (1 patient with glioblastoma and 1 patient with HCC). The SAE profile seems to differ when LY2157299 is used in patients with glioblastoma, MDS, and HCC, indicating a possibility that reporting rates are influenced by the underlying disease and there have been no trends or signals noted in the reported SAEs.

The most common TEAEs (≥10%) for LY2157299 monotherapy are fatigue (19%), anemia (18%), abdominal pain (18%), edema peripheral (15%), nausea (15%), asthenia (14%), diarrhea (14%), vomiting (14%), abdominal pain (12%), headache (12%), constipation (10%), decreased appetite (10%), and pruritus (10%). Most of these AEs were of mild or moderate severity.

The addition of LY2157299 to standard cancer treatments appeared to have no effect on the established toxicity profile of these standard therapies.

Extensive cardiac safety monitoring has been conducted in all clinical studies, and available data has shown no indication of a LY2157299-related cardiac toxicity.

The intermittent dosing regimen of 14 days on treatment with LY2157299 followed by 14 days off treatment (1 cycle = 28 days) that has been used in clinical development to date appears to be well tolerated with no clinically significant valvulopathies or aneurysms reported or observed at dosages of up to 300 mg/day.

For additional details, please refer to the LY2157299 IB, Section 6.

5.1.5.2. JBAK: Brief Summary of Results to Date

At the time of Amendment (e), Part A and Part B of the study have completed. A total of 149 patients were enrolled (109 in Part A and 40 in Part B). Eighty-five percent of patients were male and the median age was 65 years. Fifty-six percent of patients had an ECOG performance status (PS) of 0 and 44% had a PS of 1. Eighty-six percent of patients had a Child-Pugh Class A score and 14% had a Class B score. Etiology of disease was a follows: hepatitis C 24%, hepatitis B 20%, alcohol 20%; multiple 9.4%. Overall, 83% of patients had received prior sorafenib. Eleven patients discontinued treatment due to AEs: 8 were considered related to study treatment. Grade 3/4 AEs possibly related to treatment were observed in 26 (17%) patients. Of these AEs, neutrophil count decrease was observed in 4 patients. Anemia, hypoalbuminemia, decreased bilirubin, fatigue and embolism were observed in 2 patients each. All other AEs occurred in just 1 patient. Median TTP was 11.9 weeks (95% CI: 6.3, 12.6) in Part A and 18.0 weeks (95% CI: 10.0, 24.0) in Part B. Median OS was 31.4 weeks (95% CI: 22.9, 40.6) in Part A and 73.0 weeks (95% CI: 45.4, 104.7) in Part B. The median OS for the overall population was estimated as 40.4 weeks (95% CI: 31.1, 52.4) (Giannelli et al. 2016).

Enrollment into Part C has completed and maturation of the data is awaited. Enrollment is ongoing in Part D of the study.

5.1.5.3. Rationale for the Study

The scientific justification of investigating LY2157299 in HCC is compelling based on the role of TGF-β in the process of fibrosis and cirrhosis leading to HCC. The evidence of antitumor effects in several models with TGF-β inhibitors, such as LY2109761 and LY364947, suggest that LY2157299 will have activity in HCC. Also, the relatively favorable toxicity profile differentiates LY2157299 from other kinase inhibitors with their characteristic cardiovascular and cutaneous toxicity. Therefore, it is anticipated that LY2157299 will:

- Increase immunecompetence in HCC patients
- Show increased antitumor activity due to a reduction in fibrogenesis, remodeling, neoangiogenesis, and invasiveness

In addition to the scientific rationale and the expected improvements, the study is justified because of the following reasons:

- LY2157299 has shown a favorable short- and long-term toxicity profile in Study JBAH.
- No indication of cardiac insufficiency.
- Three Grade 3 to 4 events (CTCAE v 3.0) (thrombocytopenia, thromboembolism, ischemic stroke) possibly related to study drug occurred in Study JBAH in patients who received LY2157299 treatment.
- Evidence of tumor responses while patients were treated with single-agent LY2157299 in Study JBAH, the study in GBM patients.
    - Two patients had complete responses (CRs) and 3 patients had partial responses (PRs). Three patients were treated for more than 20 cycles (updated information in the IB).
- Clinical exposures achieved in Study JBAH are 1.9-fold below a no-observed-effect level for cardiac toxicity in the rat (most sensitive species for cardiac effects) suggesting clinical activity can be achieved at exposures lower than those required to elicit toxicity in nonclinical species.

The proposed immunomodulatory as well as anti-invasive properties of LY2157299 suggest that a clinical investigation in the first-line setting of patients with HCC is promising. Hence, it may be acceptable to treat patients with LY2157299 even before they are considered to receive sorafenib or other antivascular agents.

In summary, the combination of a well-tolerated agent such as LY2157299 in a disease with high unmet medical need, justifies the evaluation of this agent in the first- and second-line treatment of HCC. Thus, the overall benefit/risk profile is acceptable in this setting.

5.1.6. Rationale for Amendment (a)

The protocol is amended for the following reasons:

- Modification and clarification of inclusion/exclusion criteria taking into account updated safety information of LY2157299 and the patient population with hepatocellular carcinoma:
    - Expand inclusion criteria to Child–Pugh Class B7 as these patients are similar to Child-Pugh A patients and the current bilirubin limits for inclusion criteria include B7 patients.
    - Allow previous liver transplant patients because of the favorable safety profile of LY2157299 and because the absence of drug-drug interaction as determined with enzyme-inducing anti-epileptic drugs (EIAEDs) and proton pump inhibitors (PPIs).
    - Allow patients with lower platelet levels due the favorable safety profile of LY2157299.
    - Allow patients with hormone-refractory prostate cancer stable on gonadotropin-releasing hormone (GnRH), and patients with breast cancer stable on antiestrogen therapy to continue treatment while enrolled in the study, as these patients have their disease controlled and their condition is unlikely to interfere with the aim of the present study.
- To help investigators decide who may be considered sorafenib ineligible patients, a tool is provided (Attachment 14).
- Addition of serum markers for hepatocellular carcinoma and hematology subset for T cell on T regulatory cells.
- To remove the requirement for administration of Functional Assessment of Cancer Therapy, Hepatobiliary (FACT-Hep) questionnaire on Cycle 1, Day 1 as this procedure was considered redundant.
- To add the requirement for patients who are to have Day 15 PK to omit the evening dose on Day 14, so as to allow for a 24-hour time period between the Day 14 morning dose and the Day 15 PK sample. This was omitted from the original protocol version in error.
- To clarify and update the details of the supplied clinical trial material.
- To add confirmation that local laboratory results may be used to determine patients' eligibility.
- To clarify that the second interim analysis is planned after 40 patients have been enrolled into each dose cohort and have been actively followed for 3 months or until progressive disease or death have been observed.
- To provide corrections and clarifications within the Study Schedule (Attachment 1).

5.1.7. Rationale for Amendment (b)

The protocol is amended for the following reasons:

As part of the continuous monitoring of safety, PK, and laboratory markers in patients with HCC, the sponsor noted that patients are staying on study beyond 4 months. Furthermore, the 300 mg/day dose appears to have no evidence of increased toxicity. There appears to be no difference in the number of patients at the 160-mg/day and the 300-mg/day dose who stayed beyond 4 months. In addition, in all other ongoing trials with LY2157299, the dose of 300 mg/day was selected for future clinical development.

Preliminary PK data from the first interim analysis (n=20 patients) suggest that patients administered 300 mg/day have higher exposures than previously observed for the same dose level (Study JBAH) during the treatment period. LY2157299 appears to be fully eliminated after the 14-days off period of a cycle (additional PK sampling is added to study the clearance of LY2157299). The lowest exposure level (ie, most conservative) in the most sensitive nonclinical species administered LY2157299 in a clinically relevant dosing schedule (2 weeks on/2 weeks off) in which cardiac effects were observed was 24 μg*hr/mL (Table JBAK.2). The findings at this dose level (150 mg/kg) consisted of a single male rat (n=10/group) with minimal inflammation in the aortic valve and ascending aorta. Administration of 300 mg/day to patients with HCC may result in higher than anticipated exposures; however, due to the clinical safety profile observed thus far and the benefit:risk in this patient population, this approach is considered acceptable.

Because of these reasons and the lack of substantial evidence that the 160-mg/day dose is superior to the 300-mg/day dose, the dose of 300 mg/day is selected for the continuation of this trial.

For Part B, it was decided to evaluate the effects of LY2157299 in patients with AFP <1.5x upper limit of normal (ULN) to have an overall assessment of LY2157299 efficacy in all HCC patients. At the time of the decision to focus on the 300-mg/day dose, 74 patients were randomized.

The study design will be modified as follows:

- Part A: Evaluation of LY2157299 in Child-Pugh A or B7 patients with AFP ≥1.5x ULN. After stopping the 160-mg/day dose arm, all newly enrolled patients will be treated at the 300-mg/day dose.
- Part B: Evaluation of LY2157299 in Child-Pugh A or B7 patients with AFP <1.5x ULN

For Part C, patients with Child-Pugh B7 or B8 status do not have any therapeutic options. Sorafenib approval in HCC was granted after evaluation in patients with Child-Pugh A status (Llovet et al. 2008). Given the safety profile of LY2157299, the assessment of LY2157299 in Child-Pugh B7 or B8 patients is justified to assess potential new agents in this population.

For all patients, treatment discontinuation for progressive disease is not solely based on radiological assessments, but also considers whether the patient is clinically asymptomatic and their biomarker responses.

5.1.8. Rationale for Amendment (c)

The protocol is being amended for the following reasons:

- Based on the second interim analysis and preclinical data, Part C is being modified to evaluate the safety of sorafenib (currently the only approved systemic agent in HCC) when combined with LY2157299 in patients with first-line HCC and Child-Pugh A status:
    - Preclinical data:
      Combination of LY2157299 with sorafenib showed potentiation of sorafenib activity in vitro and ex vivo study. This implies the possibility that this combination may be more effective than LY2157299 alone.
    - Safety:
      The favorable safety and PK profile of LY2157299 thus far observed in HCC suggest that a combination with sorafenib may not add additional toxicity to the known toxicity of sorafenib. Furthermore, the PK profile for LY2157299 will be documented for patients receiving the combination treatment and compared with the PK profile for patients who received the monotherapy.
    - Antitumor activity of LY2157299 in first-line patients:
      Preliminary results from 20 sorafenib-naive patients (3 of whom had received brivanib as a first-line treatment and 17 who have not received any systemic treatment) treated with LY2157299 monotherapy estimated that the median TTP was 18.3 weeks, higher than TTP in second-line HCC patients. Together with the preclinical information, this justifies the evaluation of the combination in first-line HCC.

      An exploratory evaluation will compare the potential increase of TTP in patients receiving the combination therapy (LY2157299 + sorafenib) to the TTP observed in sorafenib-naive patients enrolled in the monotherapy part.
- Adding a treatment extension period to allow patients who are benefiting from study treatment to continue the same study treatment once study endpoint is met.
- To provide corrections and clarifications within the follow-up safety assessments and Study Schedule.

5.1.9. Rationale for Amendment (d)

The protocol is being amended to add a Part D that will allow for safety assessment of LY2157299 in combination with ramucirumab. This combination is being studied for the following reasons:

- Based on recent data, ramucirumab showed antitumor activity in HCC, including an improvement in OS for second-line HCC patients with AFP levels ≥400 ng/mL (median

OS = 7.8 months for ramucirumab versus 4.2 months for placebo; OS hazard ratio = 0.67 [95% CI, 0.51–0.90]) (Zhu et al. 2014).

- Antiangiogenic treatment, such as ramucirumab, polarizes tumor-associated macrophages to reduce immune-regulatory signals and, thereby, creates an immune-supportive microenvironment to recruit and activate CD8+ T cells (Huang et al. 2012).
- Targeting the vasculature and TGF-β together may lead to greater antitumor activity by reducing angiogenesis and, at the same time, promoting antitumor immunity via TGF-β.

5.1.10. Rationale for Amendment (e)

The protocol is being amended to add a Part E that will allow the evaluation of the safety and tolerability, pharmacokinetics and efficacy of LY2157299 administered according to a 21 days on/7 days off schedule.

Across the clinical development program at the time of Amendment (e), LY2157299 has shown a favorable short- and long-term toxicity profile in different studies and activity in different tumor types.

In light of cardiotoxicity observed in nonclinical trials of LY2157299, comprehensive cardiac safety monitoring was implemented in all clinical trials of LY2157299, including Study JBAK, and has been ongoing until the time of this amendment.

Using a data cut-off date of 15 September 2015, Lilly has performed a cross-study cardiovascular (CV) safety analysis of 745 patients from 10 completed and ongoing unblinded studies of LY2157299, including patients assigned to standard of care control arms who did not receive LY2157299. This analysis included a review of CV-related TEAEs and SAEs (with a focus on patients with increased valvular insufficiency and vascular-related hemorrhage/aneurysm, as well as patients with events of heart failure) and a correlation of TEAE/SAE data with central echocardiography findings, chest CT scan and/or MRI findings, cardiac laboratory markers (BNP, cystatin C, and troponin I) and central ECG findings. The cumulative results of this cross-study analysis did not identify any concerning trends in AEs, in particular those related to valvulopathies or aneurysms.

As described in Section 5.1.4, nonclinical toxicology data have determined a no-effect level for CV lesions that is higher than the observed and anticipated exposures in Study JBAK and other clinical trials. There is also no evidence of accumulation in patients given multiple doses of LY2157299 at 150 mg BID, suggesting that daily exposures on a schedule with increased days of dosing will remain lower than the no-effect-level for CV lesions characterized in toxicology studies.

In view of these clinical and nonclinical observations, Lilly has proposed and received endorsement from the United States (US) Food and Drug Administration to explore a new treatment schedule for LY2157299 in Part E of amended Study JBAK. This schedule will dose LY215729 at 150 mg twice daily for 21 days, followed by 7 days off drug (cycle length= 28 days). The goal is to improve upon the efficacy that has been observed in patients receiving

LY2157299 on a 14 days on/14 days off schedule by increasing time on target and thereby limiting chances for tumor regrowth and resistance.

Amendment (e) also includes the provision that Part D of Study JBAK will be conducted outside of the European Union (EU) and clarification on how Part D expansion will be conducted.

Attachment 17 lists changes made in protocol amendment (e).

6. Objectives

6.1. Primary Objective

The primary objective of this study is to characterize both the TTP distributions and the effect on TGF-β-associated serum biomarkers (for example, TGF-β, AFP, E-cadherin) of study treatment in patients with HCC.

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the safety of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab in HCC patients
- To evaluate the population PK of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab
- To recommend which doses of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab to use in future trials recruiting HCC patients
- To evaluate the safety and tolerability, pharmacokinetics and efficacy of LY2157299 as monotherapy administered according to a 21 days on/7 days off schedule
- To characterize other time-to-event distributions, such as progression-free survival (PFS, based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 and modified RECIST [mRECIST], for HCC) and OS
- To estimate antitumor efficacy using response rate (RR, based on RECIST 1.1. and mRECIST, for HCC)
- To assess patient-reported outcome (PRO) measures of disease-specific symptoms and health-related quality of life (FACT-Hep)
- To explore E-cadherin, pSMAD, and β-integrin (and other markers associated with EMT transformation and the TGF-β-associated signaling pathway) presence in the original diagnostic tumor tissue and optional posttreatment tumor tissue and the correlation of this with both clinical efficacy endpoints and biomarker response
- To explore the utility of exploratory imaging techniques (for example, positron emission tomography [PET] scan, contrast echography) to assess treatment effect with LY2157299 as monotherapy and in combination with sorafenib when possible
- To explore fibrosis-related biomarkers, such as Fibrotest

7. Investigational Plan

7.1. Summary of Study Design

Study JBAK is a multicenter, randomized trial characterizing the TTP distribution of 2 dose levels of LY2157299 in patients with Child-Pugh Class A or B HCC.

Approximately 235 patients will be enrolled into the study: 109 have been enrolled into Part A, 40 into Part B, 47 into Part C, approximately 18 into Part D and approximately 23 into Part E.

Starting with Amendment (e), there are 5 parts to this study:

Parts A and B

Part A and Part B enrolled patients with Child-Pugh Class A and B7 status HCC, distinguished by baseline AFP levels, who had either progressed on sorafenib or were ineligible to receive sorafenib. Enrollment is complete with 109 patients enrolled into Part A and 40 into Part B.

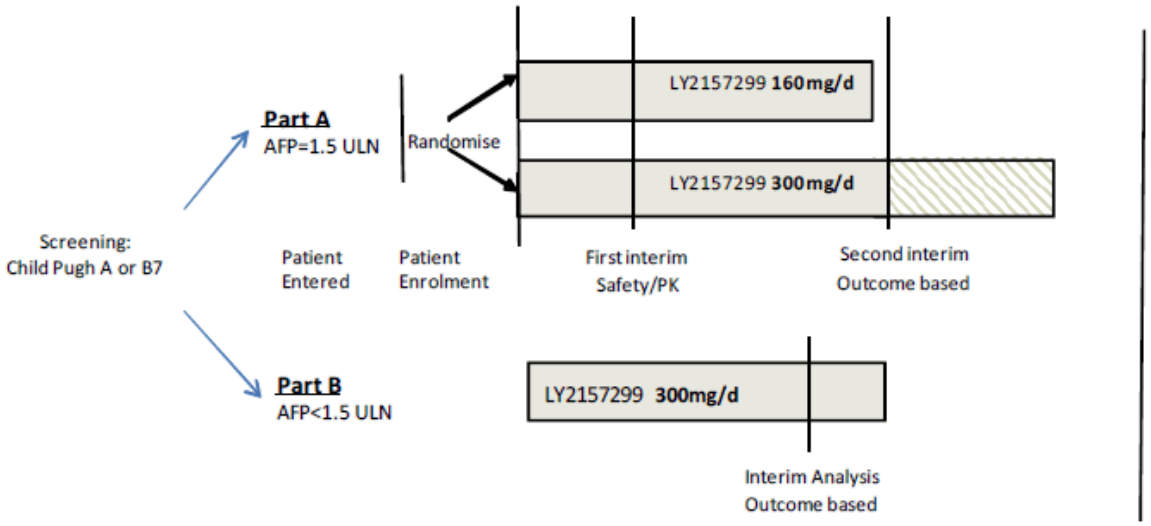
In Part A, patients with AFP ≥1.5x ULN were randomized to 2 cohorts based on initial dose of LY2157299 to be received (160 or 300 mg/day). Eligible patients were randomized to 1 of these cohorts (the 2 cohorts being balanced as far as possible for AFP levels, etiology, and whether or not sorafenib-naïve) and received LY2157299 for 14 days followed by 14 days of rest (Figure JBAK.1).

A first interim analysis for safety was planned and carried out after 10 patients per dose had enrolled and completed 1 cycle of treatment. A PK interim analysis occurred after the PK sample on Day 15 had been collected from 20 patients. The decision to continue enrollment on the 300-mg/day dose only occurred after a data review prior to the planned second interim analysis in protocol Amendment (a). Patients who were still on study treatment when this decision was made remained on their original dose unless there were safety or efficacy reasons to change their dose. For the purposes of data collection and analysis, patients whose dose was changed remained in the original cohort to which they were assigned.

At this point, Amendment (b) was implemented to continue enrolling into Cohort 2 of Part A and to initiate enrollment into Part B and included changes to the planned interim analyses.

The second planned interim analysis for Part A (based on N=106 patients, Cohorts 1 and 2) was completed after the last patient had enrolled into Cohort 2 (n=69) and started Cycle 1. Detailed information is given in Section 12.2.14 (Interim Analyses). Enrollment continued during all data reviews and interim analyses.

In Part B, patients with AFP <1.5x ULN received LY2157299 300 mg/day for 14 days followed by 14 days of rest (Figure JBAK.1). The third interim analysis occurred after 18 patients had been treated and completed 3 cycles or discontinued from study treatment. Detailed information is given in Section 12.2.14 (Interim Analyses).



Abbreviations: AFP = alpha-fetoprotein; PK = pharmacokinetics; ULN = upper limit of normal.

Figure JBAK.1. Illustration of study design for Protocol H9H-MC-JBAK Parts A and B.

Part C

Part C evaluated LY2157299 in combination with sorafenib in patients with advanced HCC and Child-Pugh Class A status who had not received previous systemic treatment. Up to 40 patients were planned to be enrolled. Enrollment is complete and a total of 47 patients have been treated.

Part C comprised a safety lead-in of 2 cohorts followed by an expansion phase with selected safe dose(s) (Figure JBAK.2). Patients enrolled in Cohort 1 were administered LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle. Three patients were planned to be enrolled in Cohort 1; if no dose-limiting toxicities (DLTs) (related to LY2157299 or combination regimen) were observed in Cycle 1, 3 patients were to be treated in Cohort 2 at LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle. If a DLT related to LY2157299 or combination regimen was observed in either cohort in the first 3 patients in Cycle 1, then that cohort was to be expanded to include an additional 3 patients. Six to 12 patients were planned to be enrolled in the safety lead-in, depending on the observed DLTs. See Section 9.1.5 for more detailed dose escalation and expansion criteria. PK sampling was conducted in Cycle 1 with the intent to assess drug-drug interactions between LY2157299 and sorafenib (Attachment 4).

Depending on the results from the safety lead-in cohorts and analysis from Parts A and B, the expansion cohort was to consist of 1 of the following:

- Single treatment group: LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle, or
- Single treatment group: LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle, or

- Two treatment groups: LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 versus LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28. Both cohorts were to be on a 28-day cycle.

Patients enrolled in the safety lead-in cohorts were to continue treatment as per that cohort.

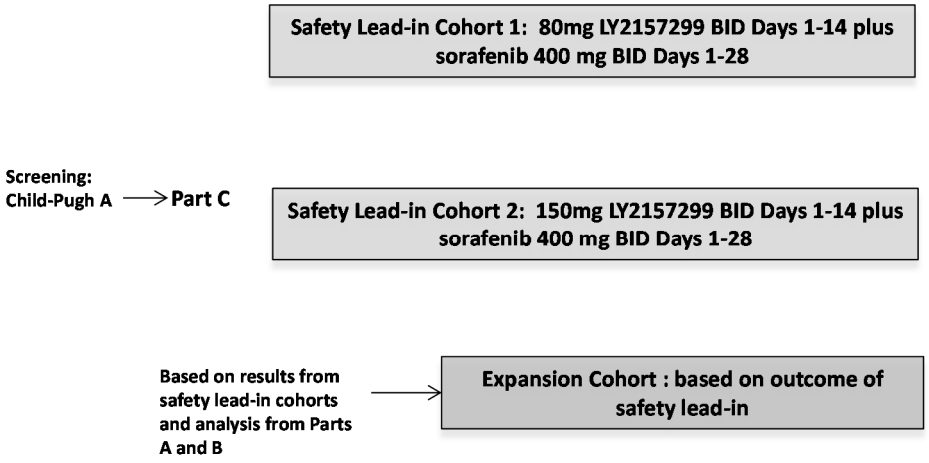


Figure JBAK.2. Illustration of study design for Protocol H9H-MC-JBAK Part C.

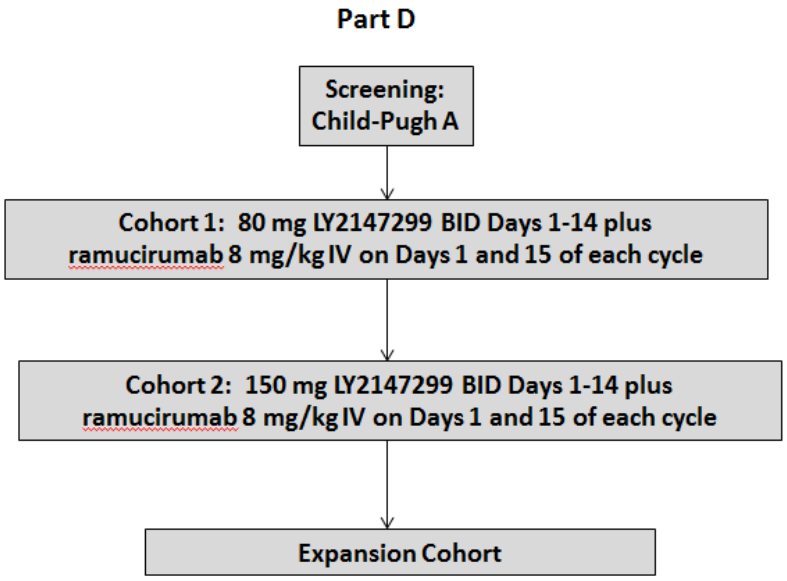
Part D

Part D will be conducted outside of the EU and will evaluate LY2157299 in combination with ramucirumab in patients with advanced HCC and Child-Pugh Class A status. Part D comprises 2 cohorts (Figure JBAK.3). Patients enrolled in Cohort 1 will be administered LY2157299 80 mg BID on Days 1 to 14 in combination with ramucirumab administered at 8 mg/kg as an intravenous (IV) infusion on Days 1 and 15 of every cycle. Approximately 18 patients may be enrolled to allow the selected dose to be expanded to approximately 15 patients in total.

Three patients will be initially enrolled on Cohort 1; if no dose-limiting toxicities (DLTs) (related to LY2157299 or the combination regimen) are observed in Cycle 1, then 3 patients will be treated on Cohort 2 at LY2157299 150 mg BID on Days 1 to 14 in combination with ramucirumab 8 mg/kg administered as an IV infusion on Days 1 and 15 of every cycle. If a DLT related to LY2157299 or the combination regimen is observed in the first 3 patients in Cycle 1 of Cohort 1, Cohort 1 will enroll an additional 3 patients. If no further DLTs are observed, Cohort 2 will be opened. If 1 or more additional DLTs are observed in Cohort 1, Part D will close. If Cohort 2 is opened and no DLTs are observed in the first 3 patients, Cohort 2 will be expanded until approximately 15 patients have been enrolled. If 1 DLT is observed in Cycle 1 in the first 3 patients in Cohort 2, another 3 patients will be enrolled. If 2 or more DLTs are observed in the first 3 patients OR 1 or more DLTs are observed in the additional 3 patients in Cohort 2, a safety review by Lilly and the investigators will occur to decide whether to expand Cohort 1. If no further DLTs are observed in Cohort 2, Cohort 2 will be expanded until a total of approximately

15 patients have been enrolled at this dose. See Section 9.1.5 for more detailed dose escalation and expansion criteria.

PK sampling will be conducted in Cycles 1 and 2 with the intent to assess changes in LY2157299 and ramucirumab exposure when administered in combination (Attachment 4).



Abbreviations: BID = twice daily; IV = intravenous.

Figure JBAK.3. Illustration of study design for Protocol H9H-MC-JBAK Part D.

Part E

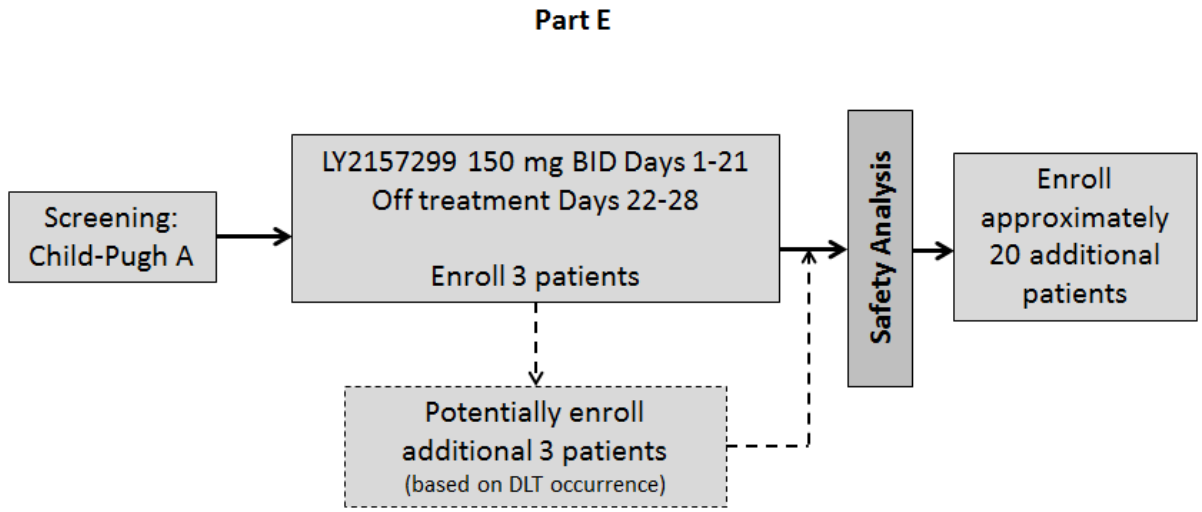
Part E will evaluate the safety, tolerability, pharmacokinetics and efficacy of LY2157299 given according to a 21 days on/7 days off schedule in patients with Child-Pugh Class A HCC who have received at least one prior line of systemic treatment or who have not received prior treatment and are ineligible for sorafenib treatment (at the investigator's discretion). Up to approximately 23 patients may be enrolled.

Figure JBAK.4 shows the Part E study design.

It is planned that Part E will initially enroll up to 3 patients. Enrollment will halt after the first 3 patients have received their first dose of treatment. If a patient discontinues study treatment within the first cycle of therapy for any reason other than a dose-limiting toxicity (DLT), that patient may be deemed unevaluable and replaced. A safety evaluation will occur after the third evaluable patient has completed one cycle of therapy. Dose-limiting toxicities will be as defined in Section 9.1.5.1. If DLTs are observed in 2 of the first 3 patients dosed, Part E will close. If DLTs are observed in 1 of the 3 patients, a safety assessment will occur after the next 3 evaluable patients have completed 1 cycle. If the schedule is deemed to be tolerable (<33% DLTs in Cycle 1 as well as consideration of the overall safety profile from later cycles), additional patients will be enrolled so that data from approximately 20 patients will be available

to better characterize the safety of the schedule and allow comparison to safety, pharmacokinetics and efficacy results in other cohorts.

Recognizing that potential CV effects may occur after the initial DLT period, patients will be regularly monitored according to a stringent schedule and as part of a trial level safety review. Trial level safety reviews will occur approximately every 3 months, beginning after the initial DLT evaluation period.



Abbreviation: BID = twice daily.

Figure JBAK.4. Illustration of study design for Protocol H9H-MC-JBAK Part E.

All Study Parts

One cycle is defined as 28 days (a minimum of 26 days and a maximum of 31 days). The treatment period for LY2157299 must be a minimum of 10 days and a maximum of 14 days (for Parts A, B, C and D) and 21 days (for Part E); the "off-treatment" period can vary to ensure an overall cycle length of 26 to 31 days). In extenuating circumstances, the "on study drug" window for LY2157299 is allowable from Day 10 to Day 14. (In Part C and D safety lead-in Cycle 1, patients must have received 14 days of LY2157299 treatment). For Part E Cycle 1, all patients must receive 21 days of treatment, followed by 7 days off treatment. If patients are not evaluable for DLT assessment and/or PK in Cycle 1 of Part C or Part D safety lead-in, or Cycle 1 Part E, the patients will be replaced.

Per patient, the screening period is no more than 4 weeks or 28 days before the first dose of LY2157299; the planned treatment duration is 6 cycles or approximately 24 weeks, but patients may continue to receive study drug if they are still benefiting from treatment in the opinion of the investigator and Lilly physician. Follow-up visits will occur approximately 30 days after the last day of study treatment and subsequently approximately every 60 days (approximately 2 months [±7 days]).

In case of the occurrence of severe toxicities in later cycles in patients treated with either LY2157299 monotherapy or LY2157299 in combination with ramucirumab or sorafenib, the sponsor will review and choose a lower dose or discontinue the patient, if necessary.

The final analysis for Parts A and B will be conducted after the study objectives for these 2 parts have been met. This is likely to be after approximately 30 deaths have occurred in Part B in order to have a reasonable estimate of overall survival in this patient group (AFP <1.5x ULN).

Part C will be considered complete and the final analysis initiated once 85% of events for survival analysis in the expanded cohort in Part C have occurred.

Part D will be considered complete and the final analysis initiated after the last patient has discontinued from study treatment and completed at least the 30-day follow-up visit [Visit 801].

Part E will be considered complete and the final analysis initiated after the last patient has discontinued from study treatment and completed at least the 30-day follow-up visit [Visit 801].

At the time all parts of the study are considered complete, the study will be considered complete and those patients still on treatment may enter the treatment extension period and continue to receive the study treatment (see Section 7.1.1).

All patients will be followed for OS until study completion.

End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study (this includes all patients who enter the extension period). The European Union (EU) has additional reporting requirements associated with the end of study. Consult regional standard operating procedures (SOPs) for further information.

7.1.1. Extension Period

After study completion (i.e., study objectives met, see Section 7.1), all patients who are on study treatment (LY2157299 alone or LY2157299 with sorafenib in Part C, LY2157299 with ramucirumab in Part D, or LY2157299 alone in Part E) and who are eligible for the extension period may continue to receive study treatment until one of the criteria for treatment discontinuation is met (Section 8.3.1). Patients who are no longer on study treatment at the time of study completion and who have completed at least the 30-day follow-up visit (V801) will be discontinued from long-term follow-up and therefore reach the end of the study, unless they are being followed due to unresolved safety concerns. Lilly will notify investigators when the extension period begins.

During the extension period, all AEs and study drug exposure will be reported on the case report form (CRF). SAEs will also be reported on the CRF and to Lilly Global Patient Safety (see Section 10.2.1.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

All patients in the extension period will be treated following the Study Schedule (see Attachment 1). This will ensure that appropriate risk/benefit assessments are conducted for all patients.

The patient's participation in the extension period will end after study drug(s) is discontinued. The date and reason for treatment discontinuation will be collected on the CRF. Data will be collected until 30 days after the patient has been discontinued from study treatment and at this point, the patient will have ended the study. If the patient dies within the 30-day follow-up period, the reason for study discontinuation will be "Death", and the cause and date of death recorded. Otherwise, the reason for study discontinuation will be noted as "Completed". There will be no long-term post-discontinuation follow-up period for these patients, unless any safety concerns have not resolved. Requests for updates on survival may occur.

After the last of the patients in the extension period has completed their 30-day follow-up period, an addendum report will be written listing the details of data collected from patients entered in this phase. The addendum report will not be delayed due to any patients continuing in long-term follow-up, but will note those patients still in long-term follow-up due to unresolved safety issues.

7.2. Discussion of Design and Control

Part A of this open-label, multicenter, multi-country Phase 2 study of patients randomized to receive 1 of 2 doses of LY2157299 is an appropriate design for assessing antitumor activity and tolerability in an HCC patient population with no alternative therapy options, including patients who the investigator decides not to give sorafenib based on its toxicity profile, the condition of the patient, the institutional practice guidelines (see guidelines in Attachment 15), or other reasons that justify not administering sorafenib.

The requirement of including patients with elevated AFP (≥1.5 x ULN) in Part A is based on previous studies suggesting that patients with elevated AFP may also have increased levels of TGF-β1 and thus have an activated TGF-β pathway. The enrollment of patients with AFP <1.5 x ULN into Part B, will allow a comprehensive assessment of LY2157299 efficacy in all HCC patients. Patients will be enrolled into Part A or B based on the local AFP assessment. For the final study assessment, the centrally collected AFP values will be used. At enrollment, the local AFP value may be higher or lower than the centrally-assessed AFP values and this will not constitute a protocol violation.

Part C will allow safety and efficacy assessment of LY2157299 combination with sorafenib as first-line treatment for HCC. Sorafenib is the approved agent for first-line treatment of HCC.

Part D will allow a safety assessment of LY2157299 in combination with ramucirumab.

Part E will allow assessment of the safety and tolerability, pharmacokinetics and efficacy of LY2157299 administered according to a 21 days on/7 days off schedule, as well as comparison of these endpoints to that observed in patients on the 14 days on/14 days off schedule. At least approximately 20 patients must complete 21 days of therapy in order to have sufficient information to assess tolerability of the regimen.

8. Study Population

8.1. Inclusion Criteria

[1] Have histological evidence of a diagnosis of HCC not amenable to curative surgery.

[2] Are Child-Pugh Class:

- Parts A and B: A or B7 (see Attachment 5)
- Parts C and D: A
- Part E: A

[3] Have serum AFP:

- Part A: ≥1.5x ULN
- Part B: <1.5x ULN

Criterion [3] applies for Parts A and B only.

[4] Have the presence of measurable disease as defined by the RECIST 1.1 (Eisenhauer et al. 2009) (see Attachment 8). A lesion that has been previously treated by local therapy will qualify as a measurable or evaluable lesion if there was demonstrable progression following locoregional therapy.

[5] Are age ≥18 years.

[6] Have given written informed consent prior to any study-specific procedures.

[7] Have adequate organ function including:

- Hematologic: absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥50 x 10^9/L, and hemoglobin ≥8 g/dL.
- Hepatic: bilirubin ≤2.5x ULN; alanine transaminase (ALT) and aspartate transaminase (AST) ≤5x ULN. Prothrombin time (PT) international normalized ratio (INR) ≤2.3; or PT limit is 6 seconds above control
- Renal: serum creatinine ≤1.5x ULN or calculated creatinine clearance (CrCL) >45 mL/min (see Attachment 9).

Note: Small differences from the outlined laboratory values will be deemed as consistent with the protocol requirements provided that the following criteria are met: are isolated, are transient, and are not reflective of a medical condition in the opinion of the investigator. Such differences are often a result of biological or laboratory equipment variability. To confirm that these results are within biological or laboratory equipment variability, repeat laboratory/hematological tests should be done prior to dosing the patient on Cycle 1 Day 1.

[8] Have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (see Attachment 3).

[9] Have:

In Parts A and B:

- received sorafenib and have progressed or were intolerant to sorafenib, or
- are ineligible for sorafenib treatment (at the investigator's discretion).

In Part C: not received previous systemic treatment.

In Part D:

- received sorafenib and have progressed or were intolerant to sorafenib, or
- are ineligible for sorafenib treatment (at the investigator's discretion), or
- have not received prior systemic treatment (at the investigator's discretion).

In Part E:

- received at least one prior line of systemic therapy, or
- not received prior treatment and are ineligible for sorafenib treatment (at the investigator's discretion).

[10] In Parts A, B, and D and E: have discontinued sorafenib for at least 2 weeks.

[11] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[12] Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the trial and for 3 months following the last dose of study drug.

[13] Females with childbearing potential must have had a negative serum pregnancy test ≤7 days prior to the first dose of study drug.

[14] Are able to swallow capsules or tablets.

8.2. Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply:

[15] Are currently enrolled in, or discontinued within the last 28 days from, a clinical trial involving an investigational drug or device or not approved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[16] Known HCC with fibro-lamellar or mixed histology.

[17] Presence of clinically relevant ascites.

[18] Liver transplant requiring increased immunosuppressive therapy. (Patients on maintenance immunosuppressive therapy after liver transplant are eligible for Parts A and B. Rapamycin analogues are not allowed.)

[19] Have received >1 line of systemic treatment in Parts A, B, and D.

[20] Have moderate or severe cardiac disease:

a) Have the presence of cardiac disease, including a myocardial infarction within 6 months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, or uncontrolled hypertension (see Attachment 11).

b) Have documented major ECG abnormalities at the investigator's discretion (for example, symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree atrioventricular block, bundle-branch blocks, ventricular hypertrophy, or recent myocardial infarction).

c) Have major abnormalities documented by echocardiography with Doppler (for example, moderate or severe heart-valve-function defect and/or left ventricular ejection fraction [LVEF] <50%, evaluation based on the institutional lower limit of normal). For additional details, refer to echocardiography protocol (see Attachment 12).

d) Have predisposing conditions that are consistent with development of aneurysms of the ascending aorta or aortic stress (for example, family history of aneurysms, Marfan Syndrome, bicuspid aortic valve, evidence of damage to the large vessels of the heart documented by computerized tomography [CT] scan with contrast).

[21] Have serious preexisting medical conditions that, in the opinion of the investigator, cannot be adequately controlled with appropriate therapy or would preclude participation in this study.

[22] Females who are pregnant or lactating.

[23] Have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix) unless in complete remission and off all therapy for that disease for a minimum of 3 years.

At the discretion of the investigator, hormone-refractory prostate cancer patients who are stable on GnRH agonist therapy and breast cancer patients who are stable on antiestrogen therapy (for example, an aromatase inhibitor) may have that treatment continued while they are enrolled in this study.

[24] Have active infection that would interfere with the study objectives or influence study compliance.

[25] For Part C, have a known hypersensitivity to sorafenib or its excipients.

[26] For Part D, have a serious illness or medical condition(s), including but not limited to the following:

a) The patient has undergone major surgery within 28 days prior to randomization or has undergone central venous access device placement within 7 days prior to randomization.
b) The patient has uncontrolled arterial hypertension ≥150 / ≥90 mm Hg despite standard medical management.
c) The patient is receiving ongoing therapy with nonsteroidal anti-inflammatory agents (NSAIDs) (eg, indomethacin, ibuprofen, naproxen, nimesulide, celecoxib, etoricoxib, or similar agents) or other antiplatelet agents (eg, clopidogrel, ticlopidine, prasugrel, dipyridamole, picotamide, indobufen, anagrelide, triflusal, or similar agents). Aspirin at dosages up to 100 mg/day is permitted.
d) The patient is receiving therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents. Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that the coagulation parameters defined in the inclusion criteria are met.
e) Uncontrolled thrombosis (including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within 6 months prior to randomization) or bleeding.
f) The patient has experienced any Grade 3 or 4 gastrointestinal bleeding or any variceal bleeding episode in the 3 months prior to randomization requiring transfusion, endoscopic or operative intervention (patients with any bleeding episode considered life-threatening during the 3 months prior to randomization are excluded, regardless of transfusion or intervention status). Patients who have esophageal or gastric varices that require immediate intervention or represent a high bleeding risk in the opinion of the investigator or consulting gastroenterologist or hepatologist are excluded.
g) Elective or planned major surgery to be performed during the course of the clinical trial.
h) Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to randomization.
i) Known allergy or hypersensitivity to monoclonal antibody treatment or any components used in the ramucirumab drug product preparation.
j) The patient's urinary protein is >1+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates ≥2+ proteinuria, then a 24-hour urine must be collected and must demonstrate <1000 mg of protein in 24 hours to allow participation in the study.
k) The patient has either a history of or current hepatic encephalopathy or current clinically meaningful ascites. *Clinically meaningful ascites* is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [15] eliminates drugs that cannot be mapped to a standard drug dictionary or for which little data are known to analyze the potential relationship of AEs or drug interactions.

Exclusion Criterion [20] excludes patients with compromised cardiac function that could be at risk when receiving LY2157299. Based on the nonclinical toxicology assessment, patients with cardiac insufficiency or damage to large vessels of the heart will be carefully screened. All moderate and severe cases of cardiac insufficiency will be excluded. Because of the average age of most patients eligible for this study, mild or minimal cardiac disease is commonly present, and therefore these patients will not be excluded (Singh et al. 1999). If CT scan of the chest cannot be performed, MRI can be used as an alternative imaging procedure.

Inclusion Criterion [14] ensures that patients are able to swallow the study medication LY2157299.

Exclusion Criterion [22] excludes patients who are pregnant or breast feeding. This is appropriate as there are no data available that can provide safety estimates for fetal development or the impact of LY2157299 on infants.

Exclusion Criteria [23], [24], and [25] provide for patient safety.

Exclusion Criterion [26] incorporates exclusions for ramucirumab for Part D based on clinical experience.

8.3. Discontinuations

8.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient is discontinued from the study drug but can be allowed to continue in the study in order to provide the follow-up data needed for the analysis of the entire intention-to-treat (ITT) population. An exception may be granted in rare circumstances because HCC patients have a serious or life-threatening condition for which there is no effective alternative therapy and, in the opinion of the investigator, is receiving benefit from study drug. In these rare cases, the investigator must obtain documented approval from Lilly to allow the patient to continue to receive study drug.

In addition, patients will be discontinued from the study drug in the following circumstances.

- The patient has evidence of objective progressive disease (radiological assessments by RECIST v1.1 or mRECIST and/or is clinically symptomatic). The important decision in determining whether or not a patient can continue on study drug could be based on their clinical symptoms, even if the patient has progressive disease based on radiological evidence. The investigator may also take into consideration biomarker responses.
- Enrollment in any other clinical trial involving use of an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.

- The investigator decides that the patient should be withdrawn. If this decision is made because of an SAE or a clinically significant laboratory value related to the study drug, the study drug is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately.
- The patient requests that he/she be withdrawn from the study drug.
- The study drug has shown unacceptable toxicity.
- The patient becomes pregnant or fails to use adequate birth control (for women with reproductive potential).
- The patient is noncompliant with study procedures, including being noncompliant with respect to taking study drug (see Section 9 on compliance).
- The patient for any reason requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.
- The investigator or 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).

8.3.2. Discontinuation of Study Sites

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

8.3.3. Discontinuation of the Study

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

9. Treatment

9.1. Treatments Administered

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent to the patient, verifying that instructions are followed properly, maintaining accurate records of study-drug dispensing and collection, and returning or destroying all unused medication to Lilly or its designee at the end of the study as requested.

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

Patients will keep a study diary to document that they are taking LY2157299 (Parts C, D and E) and sorafenib (Part C only) correctly.

A treatment delay at the start of a cycle (Day 1) of no more than 3 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not counted as a protocol violation.

9.1.1. Parts A and B

These parts involve characterization of 160 mg LY2157299/daily and 300 mg LY2157299/daily administered orally in Child-Pugh Class A or B7 HCC patients. Table JBAK.3 shows the treatment regimens.

Table JBAK.3. Treatment Regimens for Parts A and B

LY2157299	Daily Dose	Schedule	Time of Day
Part A (Cohort 1)	80 mg BID LY	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
Part A (Cohort 2) and Part B	150 mg BID LY	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.

Abbreviations: BID = twice daily; LY = LY2157299; PK = pharmacokinetic.
Note: For patients who will have a Day 15 PK sample taken, the evening dose on Day 14 will be omitted to allow for a 24-hour time period between the Day 14 morning dose and the Day 15 PK sample.
In extenuating circumstances, the 'on study drug' window is allowable from Day 10 to Day 14.

9.1.2. Part C

Part C comprises a safety lead-in of 2 dose-escalation cohorts followed by an expansion phase with selected dose(s). This part involves characterization of LY2157299 administered at either 80 mg BID or 150 mg BID for 14 days followed by 14 days off and sorafenib 400 mg BID for 28 days administered orally to Child-Pugh Class A HCC patients. LY2157299 and sorafenib need to be taken at the same time, within a 15-minute window. A cycle is defined as 28 days. Table JBAK.4 shows the proposed dose levels and schedule for Part C.

Depending on the results from the safety lead-in cohorts and analysis from Parts A and B, the expansion cohort will consist of one of the following:

- Single treatment group: LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle, or
- Single treatment group: LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle, or
- Two treatment groups: LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 versus LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28. Both cohorts will be on a 28-day cycle.

This decision will be made by the sponsor. Patients enrolled in the safety lead-in cohorts may continue treatment as per that cohort.

Table JBAK.4. Treatment Regimens for Part C

	Daily Dose	Schedule	Time of Day
Safety lead-in Cohort 1	80 mg BID LY plus	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
	400 mg BID sorafenib	Daily	Take in the morning and evening with LY dose
Safety lead-in Cohort 2	150 mg BID LY plus	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
	400 mg BID sorafenib	Daily	Take in the morning and evening with LY dose
Expansion cohort	Recommended LY dose(s) from safety lead-in plus	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
	400 mg BID sorafenib	Daily	Take in the morning and evening with LY dose

Note: For patients who will have a Day 15 PK sample taken, the evening dose on Day 14 will be omitted to allow for a 24-hour time period between the Day 14 morning dose and the Day 15 PK sample.
In extenuating circumstances, the "on study drug" window for LY2157299 is allowable from Day 10 to Day 14.
Abbreviations: BID = twice daily; LY = LY2157299; PK = pharmacokinetic.

9.1.3. Part D

Part D comprises 2 dose-escalation cohorts and involves characterization of LY2157299 administered at either 80 mg BID or 150 mg BID for 14 days followed by 14 days off and ramucirumab 8 mg/kg on Days 1 and 15 of each cycle administered as an IV infusion over approximately 60 minutes (maximum infusion rate: 25 mg/min). On Day 1 of each cycle, LY2157299 should be taken within 30 minutes before the start of ramucirumab treatment.

LY2157299 should be taken mornings and evening approximately 12 hours apart; ramucirumab should be given in the mornings.

A cycle is defined as 28 days. Table JBAK.5 shows the proposed dose levels and schedule for Part D.

Table JBAK.5. Treatment Regimens for Part D

	Dose	Schedule	Time of Day
Cohort 1	80 mg BID LY plus	Daily by oral administration 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
	8 mg/kg ramucirumab	Days 1 and 15 each cycle by IV administration (given over 60 min)	On Day 1 of each cycle, morning within 30 min of LY2157299 administration; on Day 15 of each cycle, morning
Cohort 2	150 mg BID LY plus	Daily by oral administration 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
	8 mg/kg ramucirumab	Days 1 and 15 each cycle by IV administration (given over 60 min)	On Day 1 of each cycle, morning within 30 min of LY2157299 administration; on Day 15 of each cycle, morning

Note: For patients who will have a Day 15 PK sample taken, the evening dose on Day 14 will be omitted to allow for a 24-hour time period between the Day 14 morning dose and the Day 15 PK sample.
In extenuating circumstances, the on-study-drug window for LY2157299 is allowable from Day 10 to Day 14.
Abbreviations: BID = twice daily; IV = intravenous; LY = LY2157299; min = minutes; PK = pharmacokinetic.

9.1.4. Part E

In Part E, LY2157299 will be administered orally at 150 mg BID for 21 days followed by 7 days off. A cycle is defined as 28 days. Section 9.1.5.1 details the DLT criteria that will be used. Table JBAK.6 shows the proposed dose level and schedule for Part E.

Table JBAK.6. Treatment Regimen for Part E

Dose	Schedule	Time of Day
LY2157299 150 mg BID	Daily by oral administration 21 days on/7days off	Morning and evening for 21 days and then paused for 7 days

Abbreviations: BID = twice daily.

9.1.5. Criteria for Dose Escalation (Parts C and D)

Dose escalation will be driven by safety using the 3+3 method. Both cohorts will have a minimum of 3 patients enrolled. If 1 patient in either dose level experiences a DLT within the first cycle of LY2157299 and sorafenib or ramucirumab, then up to 3 additional patients will be enrolled at that dose level. If a DLT is observed in 2 or more patients at either dose level in the first cycle, dose escalation will cease and either the previous dose level will be declared the maximum tolerated dose (MTD) or, following discussions between the sponsor and

investigators, additional patients may be treated at intermediate doses between the previous and current dose levels.

By nature of being a dose-escalation safety assessment, data will be evaluated on an ongoing basis until the MTD is determined, as defined in Section 9.1.5.1. The maximum dose of LY2157299 will be 150 mg BID. Safety data, in particular AEs, will be the primary criteria for the dose escalation. The dose will be escalated following assessment of toxicity using the standard scoring system, CTCAE version 4.0, established by the National Cancer Institute (NCI). Any AEs related to LY2157299 or sorafenib (Part C) or ramucirumab (Part D) will be considered as toxicities.

In addition, if available at the time of dose-escalation decision, PK (eg, maximum plasma drug concentration, area under the curve, and apparent systemic clearance) results will be used as secondary/supporting data for dose escalation.

Additional patients may be enrolled at a specific dose level to characterize PK/PD.

Intermediate doses levels will be explored if deemed necessary after discussion between the sponsor and investigators.

Intrapatient dose escalation is not permitted and dose escalation to the next cohort cannot occur without prior discussion and agreement between the investigator and the responsible Lilly clinical research physician (CRP). The decision will be documented in writing.

9.1.5.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition (Parts C, D and E)

A DLT is defined as an AE during Cycle 1 in Cohorts 1 or 2 that is related to the LY2157299 and sorafenib combination regimen in Part C, to the LY2157299 and ramucirumab combination regimen in Part D, or to LY2157299 administered on a 21 days on / 7 days off schedule in Part E and fulfills any 1 of the following criteria using NCI CTCAE v 4.0:

- ≥CTCAE Grade 3 nonhematological toxicity. Exceptions will be made for:
  - Nausea, vomiting, constipation, diarrhea ≤72 hours, or electrolyte disturbance that can be controlled with treatment or optimal supportive care
  - Transient (<7 days) Grade 3 elevations of ALT and/or AST, without evidence of other hepatic injury, in the setting of preexisting hepatic metastasis may not be considered a DLT if agreed by the study investigator and Lilly CRP/clinical research scientist
  - Hand-foot syndrome attributed to sorafenib only
  - Hypertension attributed to sorafenib or ramucirumab only that cannot be adequately controlled
- CTCAE Grade 4 hematological toxicity of >5 days duration
- Any febrile neutropenia

- Grade 3 or 4 thrombocytopenia with bleeding
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is possibly related to the combination regimen that requires the withdrawal of the patient from the study during Cycle 1)

As a guidance of toxicity relationship for sorafenib, please refer to Attachment 16 (safety profile for sorafenib).

For the purpose of this study, the MTD is defined as the highest tested dose in each part that has <33% probability of causing a DLT during Cycle 1.

As patients receive more cycles of treatment, investigators, together with the Lilly CRP, can declare a DLT-equivalent toxicity if a patient is experiencing increasing toxicity during treatment in later cycles (ie, other than Cycle 1), and it becomes clear that it will not be possible to complete the treatment without exposing the patient to excessive risk.

Once the MTD has been defined, that dose level will be expanded in Parts C, D and E.

If toxicities are observed in the first cycle that would meet the DLT criteria defined above for Cohorts 1 and 2 or DLT-equivalent toxicities occur in 33% or more of patients within the cohort expansions in Part C, D and E, then investigators and the Lilly CRP will assess the nature and severity of these toxicities. The safety review and decision will be documented in writing.

9.2. Selection and Timing of Doses

Room-temperature storage condition is recommended for both the tablet drug products. The tablets should remain in the primary packaging until just prior to administration.

At the discretion of the investigator, if a patient vomits within 30 minutes of taking a dose of LY2157299, the LY2157299 dose should be repeated 1 time only that same day, if nausea/vomiting permits.

LY2157299 and sorafenib (for Part C) should be taken at approximately the same time every day. Patients should take the agent preferably 1 hour before breakfast and 1 hour before dinner.

For Part D and Part E, LY2157299 should be taken mornings and evening approximately 12 hours apart. Patients should take the agent preferably 1 hour before a meal.

In Part D, ramucirumab should be given in the mornings. On Day 1 of each cycle, LY2157299 should be taken within 30 minutes before the start of ramucirumab treatment.

Tablets should be swallowed whole and not split, crushed, or dissolved for administration.

9.3. Materials and Supplies

9.3.1. LY2157299

LY2157299 will be provided as tablets in blister packs. All materials must be stored at room temperature within temperature range specified on the material label. The material will be

labeled according to regulatory requirements of the country. Should the type of clinical trial material packaging change, it will adhere to country-specific regulations.

The tablet should remain in the blister pack until just prior to administration.

9.3.2. Sorafenib

Sorafenib will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements.

9.3.3. Ramucirumab

Ramucirumab will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements.

9.4. Method of Assignment to Treatment

In Part A, patients who meet all criteria for enrollment will be randomized to receive 1 of 2 doses of LY2157299 after completing the screening at Visit 0. Assignment to dose cohorts will be determined by a computer-generated random sequence using an interactive voice response system (IVRS). The randomization method used should result in approximately equal numbers of patients in each dose cohort (no more than a difference of 4 patients between the 2 dose cohorts at any planned analysis while enrollment into both cohorts occurs). To achieve between-cohort comparability for stratification factors, the randomization should ensure as much balance as possible between AFP levels (≤400 ng/mL and >400 ng/mL), etiology (alcohol, viral hepatitis, other), and whether sorafenib naive or not, both at interim (after 20 and 80 patients have been randomized) and final analyses, the order of priority being as listed. It is important to implement a system such that treatment of eligible patients is not delayed.

The decision to stop enrolling into Cohort 1 was made based on the results from the additional data review. The remaining patients that were to be assigned to Cohort 1 (until 70 patients have been treated) who have elevated AFP levels and who meet all criteria for enrollment will be assigned by the IVRS to receive the LY2157299 300-mg/day dose (ie, transferred to Cohort 2) after completing the screening at Visit 0.

In Part B, patients who have a AFP level <1.5x ULN and who meet all criteria for enrollment will be assigned by the IVRS to receive the LY2157299 300-mg/day dose after completing the screening at Visit 0.

Enrollment into Part B will continue during the interim analysis of Part B.

In Part C, patients who have not received prior systemic treatment and who meet all criteria for enrollment will be assigned by the IVRS to receive either the LY2157299 80 mg BID or the LY2157299 150-mg BID dose after completing the screening at Visit 0.

In Part D, patients who meet all criteria for enrollment will be assigned by the IVRS to receive either the LY2157299 80-mg BID or the LY2157299 150-mg BID dosage after completing the screening visit.

In Part E, patients who have received at least one prior line of systemic therapy or who have not received prior treatment and are ineligible for sorafenib treatment (at the investigator's discretion) and who meet all criteria for enrollment will be assigned by the IWRS to receive LY2157299 150 mg BID dosage after completing the screening visit.

The IVRS will be used to assign LY2157299 clinical trial material (eg, blister packs) containing study drug to each patient. Site personnel will confirm that they have located the correct clinical trial material by entering a confirmation number found on the packaging into the IVRS.

9.5. Dose Adjustments

9.5.1. LY2157299

If a patient experiences any of the following events that are considered possibly related to LY2157299, LY2157299 will be omitted until the event resolves:

- ANC <0.5 x 10^9/L for longer than 7 days, or ANC <1.0 x 10^9/L with a single temperature of >101°F/38.3°C or a sustained temperature of >100.4°F/38°C for more than 1 hour or platelet count <25 x 10^9/L
- CTCAE Grade 3 or 4 nonhematologic toxicity

Nonhematological toxicity must resolve to CTCAE Grade 0, 1, or baseline (with the exception of alopecia, fatigue, skin rash, nausea, vomiting, constipation, or diarrhea that can be controlled with treatment).

Hematologic toxicity must resolve to a level that, in the opinion of the investigator, is reasonable to allow for continuation of treatment.

If dosing is delayed for more than 2 weeks, the patient should be withdrawn from the study.

For Parts A and B, patients who do recover within the 2-week time frame may have the dose reduced to 160 mg for 300-mg dose arm and to 100 mg for 160-mg dose arm.

For Parts C and D: in case of a dose delay of LY2157299, patients can continue sorafenib or ramucirumab treatment (at investigator discretion).

For Part E, patients who do recover within the 2-week time frame may have the dose reduced to 160 mg or their schedule altered after discussion between the investigator and Lilly CRP.

No patient will have his/her dose reduced more than once. Re-escalation to the previous dose is acceptable in the absence of continuing or cardiac toxicities. If subsequent dose reduction is required after re-escalation, the patient must be maintained at the reduced dose level for all remaining cycles.

If moderate or severe heart valve toxicities are observed, the patient must immediately be discontinued from the treatment (for definitions see Attachment 12, including references on the echocardiographic assessment based on the Guidelines of the American and European Societies of Cardiac Echocardiography). Exceptions to this rule must be approved by the ERBs.

9.5.2. Sorafenib

Doses will be delayed or reduced for clinically significant hematologic and other toxicities (Table JBAK.7; see Table JBAK.8 for modifications due to skin toxicity) that are related to sorafenib. In case of a dose delay of sorafenib, patient can continue LY2157299 treatment (at investigator discretion).

When dose reduction is necessary, sorafenib dosage may be reduced using the predefined dose levels:

- Dose level 1 (no reduction): 400 mg (2 x 200 mg) administered orally BID daily
- Dose level 2: 400 mg (2 x 200 mg) daily
- Dose level 3: 400 mg (2 x 200 mg) every other day
- If further dose reduction is required, the patient should be discontinued from the study.

At the discretion of the investigator, the dose may be re-escalated to the previous dose level 400 mg BID after the resolution of the AE.

Table JBAK.7. Sorafenib Dose Modifications for Hematologic and Nonhematologic Toxicities

Grade	Dose Delay	Dose Modification
Hematologic toxicities		
Grade 0-2	Treat on time	No change
Grade 3	Treat on time	Decrease 1 dose level
Grade 4	Delay[a] until ≤ Grade 2	Decrease 1 dose level
Nonhematologic toxicities (except skin toxicity)[b]		
Grade 0-2	Treat on time	No change
Grade 3	Delay[a] until ≤ Grade 2	Decrease 1 dose level[c]
Grade 4	Off protocol therapy	Off protocol therapy

Source: Llovet et al. 2008 supplementary material.

[a] If no recovery after 30-day delay, treatment will be discontinued unless patient is deriving clinical benefit.

[b] Also excludes nausea/vomiting that has not been premedicated, and diarrhea.

[c] If >2 dose reductions are required, treatment will be discontinued.

Table JBAK.8. Suggested Sorafenib Dose Modifications for Skin Toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modifications
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet that does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib dose by 1 dose level (400 mg daily or 400 mg every other day)
	4th occurrence	Discontinue sorafenib treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib dose by 1 dose level (400 mg daily or 400 mg every other day
	3rd occurrence	Discontinue sorafenib treatment

Source: FDA, 2011 (sorafenib prescribing information).

Suggested Management of Hypertension (adapted from Izzedine et al. 2009)

- Blood pressure should be checked regularly on sorafenib therapy. Hypertension should be managed in accordance with standard medical practice for sorafenib individualized to the patient's clinical circumstances (refer to local institutional guidance, other available guidelines, or Izzedine et al. 2009).
- For hypertension >140/90 and ≤160/100: Continue sorafenib. Consider adding or adjusting anti-hypertensive medications.
- For persistent (>160/100) or symptomatic hypertension: Interrupt sorafenib. Resume when blood pressure improves to ≤160/100. If persistent hypertension with optimal treatment consider decrease sorafenib by 1 dose level.
- In case of hypertension crisis (Grade 4), sorafenib should be withheld.

9.5.3. Ramucirumab

Doses will be delayed or reduced for clinically significant toxicities that are related to ramucirumab. In case of a dose delay of ramucirumab, patients can continue LY2157299 treatment (at the investigator's discretion).

9.5.3.1. Infusion-Related Reactions

Reduce the ramucirumab infusion rate by 50% for the duration of the infusion and all subsequent infusions if the patient experiences a Grade 1 or 2 infusion-related reaction (IRR) (per the NCI CTCAE). Premedication is recommended with an IV histamine H1 antagonist (eg, diphenhydramine) prior to administration of ramucirumab.

If a patient experiences a Grade 1 or 2 IRR, premedication **must** be given for all subsequent infusions. If a patient has a second Grade 1 or 2 IRR, administer dexamethasone (or equivalent); then, for subsequent infusions, premedicate with the following or equivalent medications: diphenhydramine hydrochloride (intravenously), acetaminophen, and dexamethasone.

Immediately and permanently discontinue ramucirumab for Grade 3 or 4 IRRs.

9.5.3.2. Hypertension

Monitor blood pressure during treatment with ramucirumab and treat as clinically indicated. Temporarily suspend ramucirumab for severe hypertension until controlled with medical management.

9.5.3.3. Proteinuria

Monitor for the development or worsening of proteinuria during ramucirumab therapy. If the urine protein level is ≥2+, perform a 24-hour urine collection. Temporarily discontinue ramucirumab administration if the urine protein level is ≥2 g/24 hours. Resume treatment at a reduced dose level (see Table JBAK.9) once the urine protein level returns to <2 g/24 hours. A second dose reduction (see Table JBAK.9) is recommended if a urine protein level ≥2 g/24 hours reoccurs.

Permanently discontinue ramucirumab therapy if the urine protein level is >3 g/24 hours or in the setting of nephrotic syndrome.

Table JBAK.9. Ramucirumab Dose Reductions for Proteinuria

Initial Ramucirumab Dose	First Dose Reduction to:	Second Dose Reduction to:
8 mg/kg	6 mg/kg	5 mg/kg

9.5.3.4. Hepatic Encephalopathy

In the case of a new occurrence of hepatic encephalopathy and/or hepatorenal syndrome, ramucirumab will be discontinued.

9.6. Continued Access to Study Drug

Because LY2157299 is an investigational agent, patients cannot receive LY2157299 without being in a clinical trial. Ramucirumab is commercially available for other indications, but patients with HCC cannot receive ramucirumab without being in a clinical trial. Sorafenib is commercially available within the studied indication and will not be provided by the Sponsor outside of this clinical trial.

9.7. Blinding

This is an open-label study.

9.8. Concomitant Therapy

No other anticancer therapy, immunotherapy, hormonal cancer therapy, or experimental medications will be permitted while the patients are participating in this study. Palliative radiation therapy to nontarget lesions is allowed. Any disease progression requiring other forms of specific antitumor therapy will be cause for early discontinuation of study therapy.

Immunosuppressive agents for patients who have received a liver transplant are allowed if the patient is receiving these drugs as a maintenance treatment after transplant (Perry and Neuberger 2005). Rapamycin analogues are not allowed.

During the first-in-human Study JBAH, patients received EIAEDs, such as carbamazepine, phenobarbital, or phenytoin. No apparent drug-drug interaction has been observed, consistent with the nonclinical absorption, distribution, metabolism, excretion (ADME) properties of this agent.

When sorafenib is administered, avoid concomitant use of strong CYP3A4 inducers (such as, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, St. John's wort), when possible, because inducers can decrease the systemic exposure to sorafenib. Warfarin is not recommended in coadministration with sorafenib.

For Part D, patients may not receive chronic antiplatelet therapy, including NSAIDs (eg, indomethacin, ibuprofen, naproxen, nimesulide, celecoxib, etoricoxib, or similar agents) or other antiplatelet agents (eg, clopidogrel, ticlopidine, prasugrel, dipyridamole, picotamide, indobufen, anagrelide, triflusal, or similar agents). Patients receiving therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents are excluded from participation. Anticoagulant therapy may be instituted during the course of treatment on study (following an asymptomatic or treatable deep vein thrombosis or pulmonary embolism), provided that no evidence of portal hypertension (including splenomegaly) or any prior history of variceal bleeding exists. Aspirin at dosages up to 100 mg/day is permitted.

9.9. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by direct questioning, review of diary, and counting returned tablets. Deviations from the prescribed dosage regimen should be recorded in the "Study treatment: modifications" form.

For patients who are significantly noncompliant (<80% or >120% of expected study drug taken in a visit interval), investigative sites must counsel patients on the importance of study drug compliance and drug accountability. Patients who are consistently out of the compliance range may be discontinued. A Lilly representative should be contacted upon the second instance of treatment noncompliance.

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

- Drug accountability will be emphasized at the start-up meeting.
- Drug accountability will be monitored throughout the study.
- Each patient should be instructed to return all study-drug packaging and unused material to the study site at each visit. The study site will keep a record of all drug dispensed to and returned by the patients throughout the study. Study site personnel will return or destroy (as requested) all unused study drug for all patients.
- Patients will keep a study diary to document that they are taking LY2157299 and sorafenib (if applicable) correctly.

Ramucirumab in Part D will be administered intravenously at the investigational site, under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing (Standard Laboratory Testing, Pharmacokinetics, Biomarker Analysis), and Appropriateness of Measurements

Refer to the Study Schedule in Attachment 1 for study procedures and their timing.

Terms used to describe the study periods are defined below:

- **Baseline/Visit 0**: From the time of screening to first study treatment (or discontinuation, if no treatment is given)
- **Treatment Start**: First day of study treatment
- **Study Treatment Period**: Time from treatment start to discontinuation from study treatment
- **Discontinuation from Study Treatment**: The day the patient discontinues study treatment (summary visit)
    - **Applies to patients in extension period, too**
- **Postdiscontinuation from Study Drug 30-day Follow-up Period**: The time after the patient discontinues study treatment during which follow-up data are collected. Visit 801 starts 1 day after discontinuation from study treatment and lasts 30 days (±3 days).
    - Applies to patients in extension period, too. However, for patients in the extension period, the end of the 30-day follow-up period is also the end of their study participation (unless further follow-up is required for safety reasons).
- **Long-Term Follow-up Period:** All subsequent long-term follow-up visits will occur at 60-day intervals (±7 days) (for example, Visit 802, Visit 803, etc.) until the patient meets the requirements to discontinue from the study. These are the preferred windows for follow-up visits (Visit 802 and beyond); however, if some information cannot be obtained at all or not within the specified window for Visit 802 and beyond, it will not result in a protocol violation if no cardiac toxicity requiring further cardiac monitoring was observed at V801.
    - Not required for patients in extension period (unless required for safety follow-up)

10.1. Efficacy Measures

All patients will be followed for progression and OS. Patients who come off therapy due to objective progressive disease will be followed for survival every 2 months. From Amendment (b), patients may continue on study treatment even if they have objective progression if they are clinically asymptomatic (see Section 8.3). However, it is important that the cycle response records objective progressive disease in the cycle that it occurred in order to

estimate time to tumor progression, progression free survival, and response rate without bias. These patients will then be discontinued from study treatment because of overall symptomatic deterioration (including biomarker response) or other causes. Patients who come off therapy and do not have objective progressive disease should be followed every 2 months after discontinuation from study treatment until death, including 6-weekly radiologic examinations until objective progressive disease is determined (using the same radiological scans as at baseline). Patients who progress should then be followed for survival every 2 months. Every attempt should be made to gather all information every 2 months (radiological scans and survival), even if a patient starts a new anticancer therapy. Evaluation of survival can be accomplished by telephone contact if necessary. The date any new anticancer therapy starts, either during the 30-day poststudy drug discontinuation period or long-term follow-up periods, needs to be collected. This will enable a better estimate of time-to-event data to inform future decisions in this indication as it will be based on more mature data.

It is important that protocol procedures related to collection of these data, both during the active study treatment phase and follow-up period, are followed and that dates of data collection are recorded accurately.

10.1.1. Clinical Efficacy Measures

The clinical efficacy endpoint of this study is to determine the TTP for each patient. The primary method used for objective progressive disease is determined by RECIST 1.1 (see Attachment 8), but is also assessed by mRECIST (RECIST modified for HCC) (see Attachment 15).

Please note: The mRECIST assessments should be performed according to the guidelines recommended by the American Association for the Study of Liver Diseases-Journal of the National Cancer Institute, AASLD-JNCI (Lencioni and Lovett 2010).

Each patient will be assessed by 1 or more of the following radiologic tests for tumor measurement at the times specified in the Study Schedule (Attachment 1): CT scan or MRI. In addition, for final study report analyses, a central review of all radiographic examinations will be conducted, and assessments of progression will be based on RECIST 1.1 and if applicable mRECIST.

Other clinical efficacy measures include other time-to-event variables and also RRs that will be determined by both RECIST 1.1 and mRECIST; although, the primary method will be RECIST 1.1.

Radiological assessments will be collected at the times shown in the Study Schedule. MRI and/or CT scans will be collected and stored centrally; if necessary, independent review of all or a representative sample of scans may be considered following study completion.

Changes in biomarkers' (collected as specified in the schedule of events and detailed in Section 10.3.3) response are measures of progressive disease response, and the relationship to clinical efficacy measures will be explored. These biomarkers are further defined in Section 12.2.3.

Health Outcome/Quality of Life Measures

The assessment of PROs, including disease-specific symptoms and health-related quality of life (HRQoL), will be assessed using the FACT-Hep (Attachment 10).

The FACT-Hep is a validated and reliable self-administered questionnaire with 45 items, which includes the 27-item FACT-G to assess general HRQoL and an 18-item hepatobiliary section with disease specific issues (Heffernan et al. 2002). FACT subscales, total score, trial-outcome index, and symptoms (Focal High Signal Intensity 8 [FHSI-8]) will be assessed. The FHSI-8 has a specific focus regarding the most frequent and concerning symptoms experienced by patients with hepatobiliary malignancies (jaundice, stomach pain/discomfort) and some that are associated with generalized advanced/metastatic malignancy (weight loss, fatigue) (Yount et al. 2002; Cella et al. 2000). These items were selected based on relative clinical importance ratings provided by a multinational group of 95 hepatobiliary cancer specialists.

The FACT-Hep will be administered at baseline, at every cycle starting from Cycle 2, and at discontinuation (see Study Schedule for details [Attachment 1]).

Patient-reported outcomes (PROs) instruments should be completed at the beginning of office visits, before any extensive contact and consultation with the clinician/study investigator or staff. Consultation with the clinician may bias perceptions about quality of life and symptoms and thus affect assessments.

The FACT-Hep will only be completed by patients for whom there is a validated translation in which the patient is fluent.

10.2. Safety Evaluations

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

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

The investigator remains responsible for following, through an appropriate health-care option, AEs that are serious 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.

10.2.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

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

Cases of pregnancy that occur during maternal or paternal exposures to study drug or drug delivery system 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 informed consent form (ICF) is signed, site personnel will record in the electronic case report form (eCRF) any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee via eCRF.

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

Any clinically significant findings from ECGs, labs, vital-sign measurements, other procedures, and so on that result in a diagnosis should be reported to Lilly or its designee via eCRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study drug, and/or drug delivery system via eCRF.

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

Events leading to the clinical outcome of death due to progressive disease will be included as part of the safety and efficacy analyses for this study and will not be reported to Lilly or its designee as AEs via eCRF, unless the investigator believes the event may have been caused by the study drug or drug delivery system.

10.2.1.1. Serious Adverse Events

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

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

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. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- 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 or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events (SAEs) occurring after a patient has taken the last dose of study drug will be collected for 30 days after the discontinuation from study treatment, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either study drug, or drug delivery system, or a protocol procedure.

Any SAE occurring prior to enrollment that the investigator believes may have been caused by a protocol procedure must be reported to Lilly or its designee within 24 hours of investigator awareness of the event and recorded on the eCRF.

Study-specific clinical outcomes of death from progressive disease should be reported as SAEs *only* if the investigator deems them related to use of the study drug.

10.2.2. Summary of Adverse Event/Serious Adverse Event Reporting Guidelines

Table JBAK.10 presents the reporting schedule for AEs and SAEs.

Table JBAK.10. Assessment Guide for Adverse Events and Serious Adverse Events

Timing	Types of AEs/SAEs Reported
Prestudy (Starts at the signing of informed consent and ends at the first dose of study drug)	• Preexisting conditions • All AEs/SAEs (except for patients who do NOT enroll). For enrolled patients, only AEs/SAEs related to protocol procedures should be reported.
On therapy (Starts at first dose of study drug[s] and ends at last dose of study drug[s])	• All AEs and clinically significant lab values regardless of relatedness • All SAEs regardless of relatedness (except death due to progressive disease unless the investigator also deems there to be a possible contribution related to study drug)
Initial follow-up Visit (V801) (Starts at discontinuation from study treatment and ends when end of study safety assessments are completed [30 days, ±3 days, after discontinuation from study treatment])	• All AEs and clinically significant lab values regardless of relatedness • All SAEs regardless of relatedness (except death due to progressive disease unless the investigator also deems there to be a possible relation with study drug)
Subsequent follow-up visits, if necessary	• Ongoing or new AEs/SAEs possibly related to study drug(s) or protocol procedures

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

10.2.3. Electrocardiography

For each subject, 12-lead digital ECGs will be obtained as single ECGs according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

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.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to 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 evaluation.

All digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG (including all intervals); a report based on data from this analysis will be issued to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study-report purposes.

It is recognized that ECG interpretations by the investigator (or qualified designee) and by the cardiologist at the central ECG laboratory may be different. When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator (or qualified designee) interpretation will be used for study entry and immediate subject management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report-writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

Other safety measures include assessments of physical examinations, preexisting conditions, transfusions and hospitalizations, and AEs. Patients will be assessed before each visit by using the CTCAE v4.0.

10.2.4. Echocardiograms with Doppler and Chest CT Scans

Because of the cardiotoxicity monitoring in this study, echocardiographs with Doppler and chest CT scans are being performed (see Attachment 1, Attachment 12, and Attachment 13). Echocardiography with Doppler will be locally assessed at screening for enrollment and throughout the study according to the Study Schedule (Attachment 1) for safety decisions by a physician or a person who is qualified by experience or training. The individual must be identified at each site. A central reading will be performed for the data used in the study report.

Chest CT scan with contrast of thorax and abdomen to evaluate the large vessels of the heart will be locally assessed at screening for enrollment and throughout the study according to the schedule of events (Attachment 1) for safety decisions by a physician or a person who is qualified by experience or training. Alternatively, chest and/or abdomen MRI are allowed.

If the patient has clinically significant cardiac findings at discontinuation (Visit 801), echocardiography, ECG and ECG chemistry will be repeated every 2 months for 6 months (Visits 803, 804, and 805).

If there are no clinically significant cardiac findings at discontinuation (Visit 801), 1 more echocardiography, ECG, and ECG chemistry will be performed after 2 months (Visit 802). If a patient receives another treatment, Visit 802 cardiac assessments will not be performed.

The monitoring described in the above 2 paragraphs also applies to patients in the extension period. Therefore, for these cases, the patient does not discontinue from the study at the end of the 30-day follow-up period but after the cardiac findings have either resolved or, if not resolved after 6 months, after discussions between the Lilly CRP and investigator.

10.2.5. Safety Monitoring

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

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

10.2.6. Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems 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/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

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

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

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

10.3. Sample Collection and Testing

Protocol JBAK Study Schedule (Attachment 1) lists the schedule for the specific tests performed for this study. With the exception of samples for PK testing, all samples should be collected prior to the LY2157299 dose unless otherwise specified in Attachment 1 or Attachment 4. In extenuating circumstances, blood can be drawn up to 3 days before Day 1, but the appropriate central laboratory kit for the respective new visit must be used.

10.3.1. Samples for Standard Laboratory Testing

Standard laboratory tests, including chemistry, hematology, and urinalysis panels, will be performed. A serum pregnancy test will be performed (if applicable). Other clinical laboratory tests will be analyzed by central and local laboratories. Protocol JBAK Clinical Laboratory Tests (Attachment 2) lists the specific tests that will be performed for this study. Patient eligibility is based on local laboratory results only, unless the investigator chooses to use the central laboratory for such a purpose. Central laboratory results are used for study report purposes and where appropriate for safety analyses.

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. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.3.2. Samples for Drug Concentration Measurements - Pharmacokinetics/Pharmacodynamics

Sparse samples for PK evaluation will be collected from all patients in the study as indicated in Attachment 4. The actual time of dosing on the day of sampling and the actual time of sampling for each of the samples must be collected. Dose information (dose time and amount of dose) must be collected for the day of sampling and the 2 days prior to the sampling day. This information can be obtained from the patient at the visit for blood sampling.

The sampling times in the schedule are approximate and the actual sampling time should be recorded. Instructions for the collection and handling of blood samples will be provided by the sponsor.

Plasma samples will be analyzed for LY2157299 using a validated method.

Bioanalytical samples collected to measure study-drug concentration will be retained for a maximum of 2 years following last patient visit for the study.

Additional samples will be collected for progressive disease analysis as indicated in Attachment 1.

For Cycle 1 safety assessment during the Part C safety lead-in cohorts, PK samples for both LY2157299 and sorafenib will be collected on Days 1 and 14. One morning PK sample (Day 15) will then be taken to evaluate the elimination-phase kinetics of LY2157299 during the nondosing phase of Cycle 1 (see Attachment 4). On Days 22 and 23, PK samples will be taken for evaluation of whether there was any change in sorafenib PK profile after monotherapy compared with sorafenib in combination with LY2157299. In Cycle 2, sparse PK sampling for LY2157299 and sorafenib will be performed as indicated in Attachment 4. From Cycle 3 onwards, only predose Day 1 samples will be taken.

For Cycles 1 and 2 safety assessments during Part D, PK samples for LY2157299 will be collected on Days 1, 14 and 15, and samples for ramucirumab will be collected on Days 1 and 15. One morning PK sample (Day 15 before ramucirumab dosing) to evaluate the elimination-phase kinetics of LY2157299 during the nondosing phase of Cycles 1 and 2 and one ramucirumab PK sample at end of infusion will be taken. From Cycle 3 onwards, only predose Day 1 samples will be taken.

For Part E, PK samples for LY2157299 will be collected on Days 1, 21 and 22 (Attachment 4).

10.3.3. Samples for Biomarker Analysis

10.3.3.1. Pharmacogenomic Evaluations

There is growing evidence that deoxyribonucleic acid (DNA) variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug ADME, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations allow, a blood

sample will be collected for pharmacogenetic analysis. It is a one-time collection, as noted in the Study Schedule (Attachment 1).

Samples will be stored and analysis may be performed on genetic variants thought to play a role in HCC and targets related to LY2157299 and other administered medicines including, but not limited to, genetic changes associated with metabolism and response genes to evaluate their association with observed response to LY2157299.

In the event of an unexpected AE or the observation of unusual response, the samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY2157299. These investigations may be limited to a focused-candidate gene study or, if appropriate, genome-wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The sample will be identified by the patient number (coded) and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator-site personnel.

Blood samples will be collected at the times specified in the Study Schedule (Attachment 1). Supplies required for the collection, handling, and shipment of the patients' samples will be provided by the sponsor. Samples will be stored at a facility selected by the sponsor in the US. Collection of a blood sample for genetic testing is a mandatory part of this study where local regulations allow. The blood sample for pharmacogenomics evaluation will be a 1-time collection unless the sample does not yield adequate DNA for use. It is recommended that the blood sample be taken at the baseline visit but may be taken at any time while the patient is participating in the clinical study. Genes related to safety, efficacy, PK, and/or the mechanism of action of LY2157299 may be tested. Patients will not have the option to request test results and will not receive the genetic test results.

10.3.4. Nonpharmacogenetic Biomarker Evaluation and Patient Tailoring

10.3.4.1. Sample Requirements and Preparation

Collection of samples for biomarker research is required for this study. Refer to the Study Schedule (Attachment 1) for timing of sample collection.

The research on stored samples from this study may look at the proteins or other biochemical markers to learn more about compound-specific disease states or how patients respond to or tolerate treatment with LY2157299 or other compounds/medications administered during this study. Stored samples may also be used in validating diagnostic tools or assay(s) related to patient tailoring and disease state.

At baseline, before the patient receives study drug, the following samples will be collected:

- pretreatment formalin-fixed paraffin-embedded (FFPE) tumor tissue taken from the original diagnostic tumor specimen if available (paraffin blocks or approximately 10 unstained slides cut from that block, for correlation studies of molecular markers
- optional tumor biopsy
- plasma

At Cycle 1, the following samples will be collected:

- plasma

At Cycle 2, an optional tumor biopsy will be collected.

After Cycle 2, at the time of disease progression and only if the patient is on study therapy, the following samples will be collected:

- plasma

10.3.4.2. Sample Labeling

All samples will be labeled with the same identification code assigned to the patient. This code will be used in lieu of the patient's name to protect the patient's identity.

Blood, serum, and plasma samples must be collected and shipped according to instructions provided in the central laboratory manual.

10.3.4.3. Sample Shipping and Handling

Samples will be shipped by the local laboratory to the designated research laboratories, according to the instructions in the central laboratory manual Designated research laboratories are associated with Lilly and are located in the US and EU.

10.4. Appropriateness of Measurements

There are no surrogate endpoints used in this study. All efficacy and safety assessments used in this study are standard and appropriate for an oncology study.

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 a start-up training session 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 may 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 the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

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

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

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a daily dosing schedule.

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

This study is a Phase 2 proof-of-concept study which attempts to characterize the quality and quantity of antitumor activity of inhibiting the novel target of TGF-β signaling in HCC; dose and dose schedule determination will not be exclusively dependent on the clinical response measures, but rather the clinical response measures will be used to interpret the progressive disease responses appropriately. These include safety, PK, a number of important progressive disease measures (such as AFP, plasma TGF-β1, plasma E-cadherin, and levels of cytokines, chemokines, and fibrosis-associated biomarkers) as well as clinical response measures.

Since the objectives of this study are composite in nature, it was important to ensure that the sample size was large enough for the parameters of each measure (safety, clinical response, progressive disease responses) to be estimated with sufficient precision. In addition, the sample size should allow for possible identification of subgroups of patients who may benefit from treatment with LY2157299 and those who may not, particularly with respect to using the treatment effect on the progressive disease efficacy markers.

12.1. Determination of Sample Size

This section describes how amendments to the protocol have affected the determination in sample size.

The original protocol and Amendment (a) planned to enroll 140 Child-Pugh Class A or B7 patients with HCC in this study. Each patient was randomized into 1 of 2 cohorts to receive either 160 or 300 mg/day of LY2157299. Both cohorts were proportionately balanced for 3 factors: baseline AFP levels (≤400 ng/mL, >400 ng/mL), etiology (alcohol, viral, other), and sorafenib-naive or not.

This sample size meant that if the study had completed to its maximum enrollment, there would be approximately 80% power to detect a HR of 1.5 as statistically significant at the 20% level (2-sided) between the 2 doses. This was assuming an exponential survival distribution, a 24-month accrual period, 6-month observation period after the last patient enrolled, and no loss to follow-up, and anticipation of around 129 events being observed.

There were 2 planned interim analyses. The first interim analysis assessed safety after 10 patients enrolled in each dose cohort (20 total patients) and completed 1 cycle of treatment and assessed PK when 10 patients/dose were eligible for PK assessments (all samples including the Day 15 sample). After the first interim analysis, it was decided that enrollment into both doses should continue. The second interim analysis was planned after 40 patients had enrolled into each dose cohort (80 total patients) and actively followed for 3 months or until progressive disease or death had been observed to further investigate safety and to compare the progressive disease efficacy measures between the 2 dose cohorts.

Consideration was also to be given to the number of patients who were free from progression at 3 months at the second interim analysis. Given that some of the patients included in this study may have previously progressed on sorafenib, a median TTP of 4.5 months would have been

considered promising, representing a 60% improvement over best supportive care of these patients (median TTP of 3 months). If the true median TTP in any dose group is 4.5 months or 3 months, then 63% or 50%, respectively, are expected to be free from disease progression at 3 months.

Details of the decision criteria for each of the planned interim analyses are provided in Section 12.2.14.

The first interim analysis was completed. However, an additional data review was carried out prior to the planned second interim analysis, and this was when 64 patients had received at least 1 dose of study drug and were reported in the clinical database. Of these, 44 patients had completed at least 3 cycles of treatment or discontinued from study treatment. The decision from this review was to stop enrollment into Cohort 1 (at 37 patients) and to complete enrollment of Cohort 2 (n=70 patients). In addition, the protocol was amended (Amendment [b]) to have 2, and possibly 3, parts in this study. The 2 cohorts planned in the original protocol and in the Amendment (a) were designated as Part A. Part B was to enroll 40 Child-Pugh Class A or B7 patients with HCC with AFP levels<1.5x ULN. Part C was to enroll approximately 40 Child-Pugh B7 or B8 status patients.

Therefore, the study (Amendment [b]) planned to enroll a total of 147 patients, and possibly 187 patients: 107 in Part A (37 in Cohort 1, 70 in Cohort 2), 40 in Part B, and 40 in Part C (if implemented). Given these changes, the primary objective of the study is now restricted to characterize both the TTP distributions and the effect on TGF-β-associated serum biomarkers (for example, TGF-β, AFP, E-cadherin) of the 2 doses of LY2157299 in patients with HCC with elevated AFP levels and in patients with normal AFP levels dosed at 300 mg/day, and not to carry out any formal comparisons. Rather, estimates of treatment differences between the 2 doses in Part A, and between Part A 300 mg/day and Part B and Part C patients would be provided.

Two interim analyses were planned for Amendment (b) – one after the 70 patients with elevated AFP levels had enrolled into Cohort 2 and started Cycle 1, and the second after 18 patients had enrolled into Part B and had been actively followed for at least 3 months or had discontinued from study treatment. If Part C was implemented, 1 interim analysis was planned after 18 patients had been enrolled and had been actively followed for at least 3 months or had discontinued from study treatment. Details of the decision criteria for the planned interim analyses are provided in Section 12.2.14.

The 2 planned interim analyses described for Parts A and B in Amendment (b) have been completed (December 2012 and June 2013).

With Amendment (c), the study planned to enroll approximately 190 patients: 109 patients have been enrolled in Part A (37 in Cohort 1, 72 in Cohort 2); 40 are planned for Part B, and 40 for Part C (amended to enroll Child Pugh A patients who had not received any prior systemic therapy and were to be treated with LY2157299 plus sorafenib in a safety lead-in followed by an expansion at the selected dose).

With Amendment (d) and the addition of Part D, an additional 15 patients may be enrolled. With Amendment (e) and the addition of Part E, approximately 23 additional patients may be enrolled.

The primary objective of the study now is to characterize the TTP distributions, the effect on TGF-β-associated serum biomarkers (for example, TGF-β, AFP, E-cadherin) and the relationship between biomarker response and efficacy endpoints of:

1) Each of the 2 doses of LY2157299 in second-line patients or patients ineligible to receive sorafenib with HCC who have elevated AFP levels (Part A, Cohorts 1 and 2),
2) In second-line patients or patients ineligible to receive sorafenib with HCC who have AFP levels <1.5x ULN dosed at 300 mg/day (Part B),
3) In first-line patients with HCC treated with 2 doses of LY2157299 in combination with sorafenib. If the decision in Part C is to use only 1 treatment group in the expansion cohort, the results from patients at the other dose will simply be listed.
4) In second-line patients with HCC treated with LY2157299 given for 21 days on followed by 7 days off (Part E).

For efficacy endpoints, no formal hypothesis testing based on a priori power calculations is planned; rather differences in various endpoints (eg, hazard ratios for TTP, OS) between appropriate treatment groups will be estimated. Since Part C patients are different in 2 ways from patients in Parts A and B (first-line versus second-line and treated with LY2157299 in combination with sorafenib compared to LY2157299 monotherapy, respectively), the only estimate of differences between Parts A and/or B with Part C will be between Part C and the sorafenib-naive patients from Parts A and B. The interpretation of any estimate will be considered in light of the size of this subgroup.

Data from patients from Part D and E will be summarized separately from the data in Parts A, B, and C.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

All patients who receive at least 1 dose of study drug will be evaluated for safety, efficacy, toxicity, and progressive disease endpoints. The progressive disease responses will especially focus on the AFP kinetics and the TGF-β1 levels but also include the assessments of EMT-associated markers (for example, E-cadherin) and fibrosis-related blood markers.

Patients with measurable disease will be included in summaries of tumor response. Tumor response will only be tabulated for patients who received at least 1 dose of study drug and have measurable disease at baseline.

After Amendment (b), patients are allowed to continue on study treatment at the investigator's discretion, even when objective progression is determined by radiological measurements, if they do not have overall symptomatic deterioration as well. This change should not affect the primary objective (estimation of TTP), PFS, or response rate. However, bias may be introduced in the assessment of OS, since patients prior to Amendment (b) will have discontinued based on objective progression alone. It is therefore important to capture patients enrolled in each amendment.

Patients from all sites will be pooled for the purposes of analysis. All confidence intervals of treatment effects will be provided at a 2-sided alpha level of 0.10, unless otherwise stated. Patients with Child-Pugh Class A and B7 will be considered as 1 group of patients, given the similarity of Class B7 patients to Class A patients. If all patients in Part A and Part B are second-line, Part C patients will be analyzed as a separate group. If there are some first-line patients in Part A or Part B, different subgroups may be required. Part D will be conducted outside of the EU. Data from patients from Parts D and E will be analyzed separately from Parts A, B, C.

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

12.2.2. Definition of Clinical Efficacy Measures

Anticancer therapy is considered any treatment after failure or discontinuation on LY2157299.

Best response is determined from the sequence of cycle responses assessed. For complete response (CR) or partial response (PR), best response must be confirmed. A second assessment should be performed ≥28 days after the first documentation of response. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Best response of stable disease (SD) is defined as disease that does not meet the criteria for CR, PR, or progressive disease and has been evaluated at least 1 time, at least 6 weeks after start of study treatment.

Evidence of progression is as defined in the RECIST 1.1 criteria (primary method) and mRECIST for both determining clinical response and time-to-event endpoints except for OS.

The following definitions for time-to-event measures will apply:

- OS duration is measured from the date of randomization to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS duration will be censored for that analysis at the date of last prior contact.

- PFS duration is measured from the date of randomization to the first date of progression of disease or of death from any cause. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date for a particular analysis, PFS will be censored at the date of last prior contact. PFS duration will be calculated and analyzed twice: (1) including clinical progressions of disease not based on lesion measurements, and (2) excluding clinical progressions.
- Time to progressive disease is measured from the date of randomization to the first date of progression of disease. For each patient who is not known to have had a progression of disease as of the data-inclusion cut-off date for a particular analysis, or who has died without progression of disease, time to progressive disease will be censored for that analysis at the date of the patient's last tumor assessment prior to that cut-off date. Time to progressive disease will be calculated and analyzed twice: (1) including clinical progressions of disease not based on lesion measurements, and (2) excluding clinical progressions.
- Duration of tumor response is measured from the date of the first objective status assessment of a CR or PR to the first date of progression of disease or death from any cause. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date for a particular analysis, duration of tumor response will be censored at the date of last prior contact.
- Time to treatment failure is measured from the date of randomization until the date of discontinuation of study treatment due to AE, progression of disease, or death from any cause. For each patient who has discontinued study treatment for any other reason, time to treatment failure will be censored at the date of discontinuation of study treatment. If a patient is still on study treatment as of the data-inclusion cut-off date for the particular analysis, time to treatment failure will be censored for that patient at that cut-off date.

12.2.3. Definition of Pharmacodynamic Efficacy Measures

AFP elevation is an important marker of disease progression in HCC. Hence, a treatment effect can be measured by following the kinetics of AFP reduction during the treatment period. It is estimated that a reduction of 50% over 3 months is a relevant change suggesting a treatment effect.

Less validated is the increase of TGF-β1 levels in HCC patients. However, there is a body of studies suggesting that levels above 800 ng/mL are correlated with poor clinical outcome. Hence, a reduction in TGF-β1 levels is another marker of activity of a beneficial treatment effect. Given that LY2157299 is specifically designed to reduce TGF-β-related pathology, a change in the TGF-β1 kinetics is an important proof-of-concept for the activity of LY2157299.

Finally, E-cadherin is a protein associated with the EMT. Its levels were found to be increased in aggressively growing HCC. Hence, a change in kinetics of its levels may reflect treatment effects.

12.2.4. Patient Disposition

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

- a summary of data on patient discontinuation
- a summary of data on overall qualification status of all patients
- an account of all identified protocol violations

All patients entered in the study will be accounted for in the summary. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified.

12.2.5. Patient Characteristics

Patient characteristics will include a summary of the following:

- patient demographics
- baseline disease characteristics
- preexisting conditions
- historical illness
- prior therapies
- concomitant drugs

Other patient characteristics will be summarized as deemed appropriate.

12.2.6. Concomitant Therapy

Concomitant medications will be listed and may be summarized by World Health Organization (WHO) preferred name.

12.2.7. Treatment Compliance

A summary of treatment compliance will be generated using information from drug accountability records and the patient diary. A patient will be considered compliant with the study-therapy protocol if pill counts indicate the patient took at least 80% of LY2157299 during the preceding cycle of study therapy (refer to Section 9.9).

An attempt may be made to determine how compliance to study treatment relates to observed study-related outcome.

12.2.8. Clinical Efficacy Analyses

Kaplan-Meier analysis will be performed on the observed distribution of TTP (Kaplan and Meier 1958) for each dose in Part A, Part B, Part C, Part D and Part E, with parameter estimates of the TTP median and quartiles being reported. All parameter estimates will be quoted together with their 90% confidence limits. The hazard ratio between the observed TTP distributions of each cohort in Part A will be estimated, recognizing that since 1 dose cohort did not enroll to its full

complement, the precision of the HR will be lower than originally planned. The hazard ratios between the 300 mg/day cohort in Part A and Part B cohort will also be estimated. In addition, the hazard ratio between a subgroup of sorafenib-naive patients in Parts A and B and patients in Part C may be estimated. The interpretation of any estimate will be considered in light of the size of this subgroup.

Alternative distributions of TTP times, such as exponential Weibull (estimating a shape parameter may also be considered) where median TTP and its 90% CIs will be reported. Individual parameters, such as TTP rate after specific time points (for example, after 12 months on treatment) will be estimated from the TTP distribution.

Secondary efficacy measures include other time-to-event parameters, and these will follow the same analyses as described above.

The overall response rate (ORR) for each cohort in Part A, Part B, Part C, Part D and Part E will be estimated by dividing the total number of confirmed responders by the number of patients who received at least 1 dose of study treatment. The clinical benefit rate will be estimated for each treatment group by dividing the total number of patients experiencing benefit by the number of patients who received at least 1 dose of study treatment. A patient is considered to have received benefit if they achieve a confirmed response, CR or PR, or SD per RECIST v1.1 or mRECIST. Both mean and exact confidence limits will be provided for each group (Cohort 1 and Cohort 2 in Part A, Part B, Part C, Part D and Part E, as well as estimates of differences between 2 cohorts in Part A, between Parts A and B at 300 mg/day, and between sorafenib-naive patients in Part A and Part B with those in Part C. The interpretation of any estimate in the latter comparison will be considered in light of the size of this subgroup.

Additional exploratory analyses of efficacy endpoints will be performed to assess the effect of important prognostic factors on the outcome, including, but not exclusively, baseline AFP levels (either as a continuous factor and/or categorical factor), etiology, and whether sorafenib-naïve or not. Analyses using subgroup identification methods, such as classification and regression tree (CART) (classification and regression tool) may also be carried out. The only difference between Part A and Part B patients is their baseline AFP levels, and therefore results from Cohort 2 in Part A and Part B will be combined in these analyses. Similar analyses for patients in Parts C, D and E may be carried out.

The original statistical analysis plan (SAP) was finalized prior to the first patient in the study being dosed. The amended SAP was finalized prior to the first patient in Part B being dosed. The amended SAP (version 2) was finalized prior to the first patient in Part C being dosed. The amended SAP (version 3) will be finalized prior to the first patient in Part D being dosed. An amended SAP (version 4) will be finalised prior to the first patient in Part E being dosed.

12.2.9. Pharmacodynamic Efficacy Analyses

Pharmacodynamic (PD) parameters (for example, AFP, E-cadherin, TGF-β1) will be analyzed using a mixed-effects model with patient as a random effect and dose, time of sample, and baseline values as fixed effects. Two effects of LY2157299 are of interest for changes in AFP

levels: first, whether there is evidence of a reasonably sustained (≥2 months) 50% or greater reduction from baseline (as this is considered indicative of clinical benefit) in either dose. Second, whether there is a difference of 20% in the percentage change from baseline between the 2 doses (eg, 50% reduction at 300 mg/day and 30% reduction at 160 mg/day).

Comparisons between subgroups of interest (baseline AFP [as a continuous covariate and subgroups categorized by cutoff values], etiology, and whether sorafenib-naive or not) will be carried out by either including these terms as fixed effects, including interaction terms if needed) in the above model or as separate analyses. The decision will be in part based on whether there is any evidence that the variability of data differ between the different subgroups and the actual number of patients enrolled in each subgroup. A variance-covariance structure will be added to the model as appropriate. Serum concentrations will be log transformed prior to analysis as concentration data are typically log normally distributed, and the comparisons of interest are fold differences between different groups as opposed to absolute differences. In addition to the above 2 analyses, the percentage of patients who have at least 2 cycles of reductions of at least 25% AFP levels will be provided. Percentages of patients for other cutoff values may also be provided. With the early closure of Cohort 1 in Part A and addition of Part B, the above effects of interest will be investigated by providing summary statistics and estimating differences between study Parts A and B for patients on 300 mg/day.

The association between changes in PD parameters and clinical endpoints will be explored to determine their value as predictive biomarkers of drug effect on clinical outcome.

Summary statistics for each parameter will be provided by dose, time, and subgroup of interest. Estimates of fold differences from the model (between doses for each subgroup of interest and also between subgroups of interest within each dose) will be provided together with their 95% CIs. Visual presentation of the results will be provided where meaningful.

12.2.10. Pharmacokinetic/Pharmacodynamic Analyses

The plasma concentration versus time data together with information on dosing and patient characteristics will be pooled and analyzed using a population PK analysis approach. Nonlinear mixed-effect modeling (NONMEM) will be used for the estimation of the population PK parameters of LY2157299.

All patients who have completed at least 2 days of sampling will be included in the PK analysis. LY2157299 PK will be modeled using NONMEM. These population parameters describe the average dose-concentration relationship in the target population, the influence of fixed effects (such as weight or age) on a PK parameter of interest, the interindividual variation in the PK parameter, and the residual variation in the observed concentration.

For the purposes of the JBAK study report, plasma-concentration data will be illustrated graphically and summarized descriptively. If data are sufficient, then data from patients in this study will be modeled using the population approach for characterizing LY2157299 PK. In addition, if appropriate, data from patients in this study will be combined in a PK database with data from Study JBAH and other completed studies, for population PK analysis. In Part C, Cycle 1 assessment on possible sorafenib exposure change during monotherapy and combination

will be made. In Part D, Cycle 1 and 2 assessment of the possible LY2157299 exposure and/or ramucirumab change when in administered in combination will be evaluated. In Part E, Cycle 1 LY2157299 PK profile of patients dosed for 21 days on treatment and 7 days off treatment will be characterized.

Exploratory PK/PD analyses will be conducted to identify the exposure-response (biomarker) relationship in this study. The PK and PK/PD analyses may be reported as separate stand-alone reports for this study. Additional analyses such as exposure-response using TTP and/or other appropriate clinical endpoints may be explored, if data warrant.

The version of any software used for the analysis will be documented, and the program will meet Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by global PK management.

12.2.11. Health Outcome/Quality of Life Analyses

The following will be carried out for each part separately.

Questionnaire compliance rates will be ascertained at each measurement time point until the end of study therapy including at discontinuation (Visit 801).

Summary descriptive statistics will be provided for the PRO data (FACT-Hep) at each assessment. This summary will include mean, standard deviation, median, minimum, maximum, and change from baseline. Scores will be evaluated both in aggregate (that is, median values for each study arm at a given time point) and individually, in which each patient's score on study is evaluated relative to his/her baseline score. Time to worsening of symptoms will also be evaluated, and longitudinal analyses, such as repeated measures, will be performed. FACT subscales, total score, trial-outcome index, and symptoms (FHSI-8) will be assessed per the established scoring algorithm.

Other exploratory longitudinal analyses may be performed.

12.2.12. Safety Analyses

Adverse event (AE) terms and severity grades will be assigned by the investigator using CTCAE v4.0. AE terms will also be derived from verbatims using the Medical Dictionary of Regulatory Activities.

All patients who received LY2157299 will be evaluated for safety. Safety analyses will include, but are not limited to, the following:

- all reported AEs, including seriousness, severity, and possible relationship to study drug, using CTCAE terminology and grades
- TEAEs, including seriousness, severity, and possible relationship to study drug, using CTCAE terminology and grades
- dose adjustments for any study therapy

- physical exam and other safety observations, including those specifically targeting monitoring for cardiac safety
- laboratory measures

Safety analysis may also estimate the difference in the incidence of AEs between the 2 doses and study parts, adjusting as necessary for baseline AFP levels or other important covariates.

12.2.13. Exploratory Analyses

Exploratory analyses/data mining will be carried out on imaging data, Fibrotest data, gene-expression data, rules-based medicine multi-analyte panel (MAP) data and tumor-tissue data as appropriate, investigating links between these data and clinical and PD efficacy endpoints. Other TGF-β-signaling pathway biomarkers will also be included in this analysis.

After Amendment (a), both Child-Pugh Class A patients and Child-Pugh Class B7 patients are eligible and are being treated as 1 group given the similarity between these groups of patients, but additional analyses will look at the contribution of both classes to the clinical endpoints. In addition, as of Amendment (a), patients with liver transplant on maintenance immunosuppressive therapy are eligible, and possible differences in safety and efficacy endpoints between patients with and without liver transplant will be investigated.

After Amendment (c), first-line Child Pugh A patients are included in the study. Similar analyses to those conducted for patients in Parts A and B will be carried out for patients in Part C.

Given the more limited number of patients to be enrolled in Part D and E, exploratory analyses will be carried out as appropriate.

12.2.14. Interim Analyses

There were 2 planned interim analyses in Amendment (a). The first interim analysis reviewed both safety and PK of LY2157299. Safety was assessed after 20 patients (10 patients/dose) had enrolled and completed 1 cycle of treatment. The PK interim analysis occurred after the PK sample on Day 15 had been collected from 20 patients (this was carried out after the safety review).

For enrollment to continue in either dose level, there had to be no evidence of cardiotoxicity in any patient at that dose level and no drug-related CTCAE Grade 3/4 toxicity that was not manageable. The PK of LY2157299 in HCC patients were compared to those of patients with glioblastoma observed in Study JBAH. Since only sparse sampling was performed in Study JBAK (Parts A and B), comparisons between the 2 populations were carried out by simulations (median and 20th and 80th percentiles) using the population PK model from Study JBAH.

The decision to continue was based on the following:

1. If neither dose was considered tolerable, then the study would be terminated.
2. If only 1 dose was considered tolerable, then enrollment would continue into this dose cohort, and the other dose cohort would close.

3. If the predicted 80th percentile of the distribution of AUC exceeded 10.96 (mg.h/L) for either dose, enrollment into this dose cohort may have been ceased.

Enrollment after the first interim analysis continued in both dose cohorts, and a second interim analysis was planned when an additional 30 patients had been enrolled in each arm (i.e., total of 40 patients in each arm) and had been actively followed for 3 months or progressive disease or death had been observed. This was to be after the second planned radiological assessment (planned every 6 weeks) and after the collection of biomarker (specifically AFP) samples for all patients. Any patient who was lost to follow-up or started a new anticancer therapy before 3 months had elapsed without an event being observed was not eligible for inclusion in the interim analysis.

The decision for dropping 1 of the 2 dose cohorts was to be based on a composite endpoint, including the number of patients who were free from progression at 3 months, amount reduction in AFP and other TGF-β related biomarkers from baseline (adjusting for baseline levels if needed), and safety.

For example:

1. If the observed mean percentage reduction from baseline in AFP concentrations in either cohort was more than 50%, enrollment into the dose cohort may continue.
2. If the difference in mean percentage change from baseline in AFP concentrations between the 2 doses is >20%, then the dose with the lowest reduction from baseline may be dropped after taking into consideration the observed results for E-cadherin and other TGF-β related biomarkers.
3. Either dose or both doses will be dropped if there is evidence of cardiotoxicity and/or drug-related CTCAE Grade 3/4 toxicity that is not manageable in any patient.
4. If the number of patients who are free from progression at 3 months in either dose is 21 or less, then the dose level may be discontinued.
    - This cut-off represents a risk of continuing when the true median TTP is not considered clinically meaningful over no intervention (that is, median TTP = 3 months) is 32% and of deciding not to continue when the true median TTP is considered meaningful (that is, median TTP = 4.5 months) is 11%. (Information for risks of an incorrect decision using other cutoff values will be provided in the SAP.)

Two effects of LY2157299 are of interest for changes in AFP levels – whether there is evidence of a reasonably sustained 50% or greater reduction from baseline (as this is considered indicative of clinical benefit) in either dose and whether there is a difference of 20% in the percentage change from baseline between the 2 doses (for example, 50% reduction at 300 mg/day and 30% reduction at 160 mg/day). With 40 patients enrolled at each dose cohort and an assumed within-patient coefficient of variation of 44% (data on file), there is at least 95% probability that treatment effect of 50% within a dose group will be detected as significant at the 5% significance

level. The more sensitive situation concerns the probability of detecting a difference of 20% in the percentage reduction in pre and postdose concentrations between the 2 dose groups in order to choose a dose at this stage. The power to detect a 20% difference in percentage reduction between the 2 doses is approximately 80%, at the 20% 2-sided significance level.

Analysis of the mean fold change from baseline of biomarker concentrations levels were to be estimated from a mixed-effects model with sampling time, dose and their interaction as fixed effects, baseline levels (either as a continuous variable or categorical [AFP: ≤400 ng/mL or >400 ng/mL]) as a covariate and patient as a random effect. The choice of variance-covariance structure was to have depended on the data. Biomarker concentrations were to be log transformed prior to analysis. Specific details of these analyses will be provided in the SAP.

If at the second interim analysis, when a total of 40 patients had been enrolled at each dose and followed as described, results of the comparison between the doses were still inconclusive, the decision to either continue enrollment into both doses or to choose 1 dose was to be made after discussions between the investigator, Lilly, and study statistician.

However, the planned second interim analysis described in Amendment (a) was not carried out, but an additional data review was conducted. Based on this review, the decision was to close Cohort 1 and continue enrollment until 70 patients enrolled into Cohort 2. At the time of the decision, 64 patients had been treated.

As part of Amendment (b), the second interim analysis for Part A was changed and planned to be after the 70th patient enrolled into Cohort 2 and started Cycle 1. The purpose of this analysis was to help inform the decision to prepare for further development of the compound in patients with HCC with elevated AFP levels. This analysis was completed in December 2012 (Faivre et al. 2013).

The purpose of the interim analyses in Part B (interim analysis 3) and Part C (interim analysis 4) was to prepare for further development of the compound and to inform the decision as to whether all second-line HCC patients, irrespective of baseline AFP levels (Part B), and Child-Pugh B7 or B8 status (Part C) patients may benefit from treatment with LY2157299.

The timing of the interim analyses for Parts B and C was based on assuming Parts B and C are designed as a Simon's 2-stage design with the same characteristics as used in the original protocol: where the assumption of a poor treatment is if the proportion free from disease progression is 50% at 3 months (assumes median TTP = 3 months) and a good treatment is if the proportion free from disease progression at 3 months is 63% (assumes median TTP = 4.5 months). The operating characteristics of this design are as follows: The null hypothesis is that the true response rate is 50%. In the first stage, 18 patients will be accrued and actively followed for at least 3 months or until they have discontinued. If there are 8 or fewer patients free from disease progression in these 18 patients, this may be indicative that patients with normal AFP levels are not benefiting from the treatment. The additional 22 patients will be accrued for a total of 40. The null hypothesis will be 'rejected' at the end of Parts B and C if 22 or more patients out of 40 patients in each part are observed to be free from disease

progression at 3 months. This design yields a type I error rate of 15% and power of 78% when the true response rate is 63%.

From Amendment (c), the above calculations now only applied to the third interim analysis (for Part B, completed June 2013). Given the change in strategy for Part C to enroll and treat first line Child Pugh A or B7 patients in amendment (c), only safety reviews are planned while the study is ongoing. An additional analysis may be carried out if needed to help with clinical planning of the compound for treating first-line patients.

Safety reviews for Part D are planned to determine the LY2157299 dose in combination with ramucirumab. This will be after 3 patients have completed 1 cycle of treatment in Cohort 1 (LY2157299 80 mg BID) prior to escalating to Cohort 2 (LY2157299 150 mg BID). A further safety review will be carried out after 3 patients have completed 1 cycle in Cohort 2.

In Part E, safety data will be reviewed after 3 patients have completed one cycle. If the schedule is deemed to be tolerable (<33% DLTs in Cycle 1 and consideration of the overall safety profile in later cycles), an additional 20 patients will be enrolled in order to better characterize the safety of the schedule and allow comparison to safety, pharmacokinetics and efficacy seen in other cohorts. No additional interim analyses are planned for Part E.

The timing of the final analyses for each study parts' clinical study reports and the final database lock is provided in Section 7.1.

12.2.15. Criteria for Study Termination

This Phase 2 study will be considered complete following the completion of all data collection and/or study objectives have been met (including any possible long-term "follow-up" survival analysis). The Lilly CRP will notify investigators in the event of study closure and the decision to stop collecting data.

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 patients entered into the study and to document that the patients satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

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

13.2. Ethical Review

Lilly must agree with all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations and performed in accordance with a written process approved by Lilly.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly. The ERB(s) will review the protocol as required.

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

The study site's ERB(s) should be provided with the following:

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

13.3. Regulatory Considerations

This study will be conducted in accordance with:

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

2) the International Conference on Harmonisation (ICH) GCP Guideline [E6]

3) applicable laws and regulations

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

This study is being conducted under an active US Investigational New Drug (IND) application. The US IND number is 116167.

All or some of the obligations of the sponsor will be assigned to several third-party organizations. These responsibilities include (1) ensuring that the study is conducted in accordance with Study Protocol JBAK, and (2) shipping study drug to the investigative sites.

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

13.3.1. Investigator Information

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

13.3.2. Protocol Signatures

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

13.3.3. Final Report Signature

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

The investigator with the most enrolled patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The sponsor's responsible medical officer will sign 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 JBAK Study Schedule

Parts A and B

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**1[i]**	**14[i,k]**	**1[i]**	**14[i,k]**				
Procedures																
Informed Consent	X															Informed consent must be signed prior to performing any study procedures.
Medical History		X														
Child-Pugh, Barcelona Clinic Liver Cancer (BCLC), and CLIP staging			X[h]													
Pregnancy Test			X													
Physical Exam		X		X		X			X	X	X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
Vital Signs (heart rate, blood pressure)		X		X		X			X	X	X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
CTCAE Grading		X		X		X			X	X	X		X	X	X[a]	Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
Concomitant Medications		X		X					X		X		X	X	X	Perform predose on Day 1 of each cycle in extension period.
Performance Status		X		X		X			X	X	X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**1[i]**	**14[i,k]**	**1[i]**	**14[i,k]**				
Tumor Assessment, Physical (Palpable or Visible)		X		X					X		X			X		Optional during the extension period (including extension period V801)
Imaging Procedures																
Echocardiography with Doppler[g]	X								X		X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8,…etc). Perform predose on Day 1 of each cycle in extension period
Chest CT Scan or Chest MRI		X											X	X[c]		CT scan or MRI every 6 months
Tumor Assessment, Radiological		X								X	X			X[d]	X[d]	Tumor assessment every 6 weeks starting Cycle 2, Day 14. May be performed 3 days around the scheduled date. Optional during the extension period (including extension period V801)
ECG		X							X		X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8,…etc). Perform predose on Day 1 of each cycle in extension period

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**1[i]**	**14[i,k]**	**1[i]**	**14[i,k]**				
Laboratory /Diagnostic Tests																
ECG chemistry		X							X		X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8,…etc). Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Special chemistry			X		X	X		X	X	X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Hematology			X		X	X		X	X	X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Serum chemistry			X		X	X		X	X	X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Urinalysis		X							X		X			X		Optional during the extension period (including extension period V801)
Urine C-terminal telopeptides of Type 1 collagen		X							X		X					Optional during the extension period

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**1[i]**	**14[i, k]**	**1[i]**	**14[i, k]**				
PK sampling[e]				X		X	X	X	X		X					Timed with ECG
Serum markers (AFP, AFP L3, E-cadherin, PIVKA II)		X		X		X			X	X	X	X	AFP only	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Immuno-phenotype				X					X		X			X		Optional during the extension period (including extension period V801)
TGF-β+PF4		X		X		X			X	X	X	X		X		Optional during the extension period (including extension period V801)
MAP panel		X				X				X		X		X		Optional during the extension period (including extension period V801)
Fibrotest		X				X				X		X				
aPTT/PT/ INR		X		X					X		X		X			Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Patient-Reported Outcomes																
FACT-Hep		X							X		X			X		Optional during the extension period (including extension period V801)

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**1[i]**	**14[i,k]**	**1[i]**	**14[i,k]**				
Translational Research																
Whole blood for PGx		X														
Obtained diagnostic tumor tissue, when available		X														
Optional tumor biopsy	X									X						+/- 3 days after end of treatment with LY2157299

Abbreviations: AFP = alpha-fetoprotein; aPTT = activated partial prothrombin time; C = cycle; CLIP = Cancer of the Liver Italian Program; CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; FACT = Functional Assessment of Cancer Therapy; INR = international normalized ratio; MAP = multi-analyte panel; MRI = magnetic resonance imaging; PGx = pharmacogenomics; PIVKA II = prothrombin induced by vitamin K absence; PK = pharmacokinetic; PT = prothrombin time; TGF-β = transforming growth factor beta.

a If drug-related toxicity is present 30 days after last cycle of study drug, patients must be followed up approximately every 30 days until toxicity resolution, stabilization, another therapy is initiated, or death.

b If the patient has clinically significant cardiac findings at discontinuation (V801), echocardiography with Doppler, ECG, and ECG chemistry will be repeated every 2 months for 6 months (V803, V804, and V805). If there are no cardiac findings at discontinuation (V801), 1 more echocardiography with Doppler, ECG, and ECG chemistry will be performed after 2 months (V802) unless a patient is receiving another treatment (see Section 10.2.4).

c If there were no clinically significant findings at the last assessment conducted within the 30 days following discontinuation and the patient has started another treatment, Visit 801 CT scan or chest MRI with contrast will not be performed.

d Repeat radiological scans at study discontinuation may be omitted if a patient has objective disease progression or if imaging has been performed in the previous 3 to 6 weeks.

e For details, see Attachment 4. PK sampling will be performed on Cycle 1, with a predose sample on Day 1 of Cycle 2 and all subsequent cycles.

f Follow-up consists of Visit 802 and all subsequent visits (60 days ±7 days)

g Echocardiography with Doppler can be performed up to 3 days prior to Day 1.

h Child-Pugh, BCLC, and CLIP assessment procedures can be found in Attachment 5, Attachment 6, and Attachment 7, respectively.

i To be performed predose LY2157299.

j A delay at the start of a cycle (Day 1) of no more than 3 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not counted as a protocol violation.

k In extenuating circumstances, the 'on study drug' window is allowable from Day 10 to Day 14.

l Patients on study for more than 1 year (before entering extension phase) only need tests to be performed on Day 1 of each cycle.

Part C

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Extension Period	Visit 801	Follow -up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14[i,k]**	**15**	**22**	**1[i]**	**14[i, k]**				
Procedures																				
Informed Consent	X																			Informed consent must be signed prior to performing any study procedures.
Medical History		X																		
Child-Pugh, Barcelona Clinic Liver Cancer (BCLC), and CLIP staging			X[h]																	
Pregnancy Test			X																	
Physical Exam		X		X		X					X	X			X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
Vital Signs (heart rate, blood pressure)		X		X		X					X	X			X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
CTCAE Grading		X		X		X					X	X			X		X	X	X[a]	Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
DLT assessment										X										Safety lead-in cohorts 1 and 2 only
Concomitant Medications		X		X							X				X		X	X	X	Perform predose on Day 1 of each cycle in extension period.

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Extension period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14[i,k]**	**15**	**22**	**1[i]**	**14[i,k]**				
Performance Status		X		X		X					X	X			X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
Tumor Assessment, Physical (Palpable or Visible)		X		X							X				X			X		Optional during the extension period (including extension period V801).
Imaging Procedures																				
Echocardiography with Doppler[g]	X										X				X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8…etc). Perform predose on Day 1 of each cycle in extension period.
Chest CT Scan or Chest MRI		X															X	X[c]		CT scan or MRI every 6 months
Tumor Assessment, Radiological		X										X			X			X[d]	X[d]	Tumor assessment every 6 weeks starting Cycle 2, Day 14. May be performed 3 days around the scheduled date. Optional during the extension period (including extension period V801).
ECG		X									X				X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8,…etc) Perform predose on Day 1 of each cycle in extension period.
Optional PET scan																				At discretion of the investigator.

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Extension period	Visit 801	Follow -up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14[i,k]**	**15**	**22**	**1[i]**	**14[i,k]**				
Laboratory /Diagnostic Tests																				
ECG Chemistry		X									X				X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8,…etc). Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period.
Special Chemistry			X		X	X		X			X	X		X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period.
Hematology			X		X	X		X			X	X		X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period.
Serum Chemistry			X		X	X		X			X	X		X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period.
Urinalysis		X									X				X			X		Optional during the extension period (including extension period V801).
Urine C-terminal telopeptides of Type 1 Collagen		X									X				X					Optional during the extension period.
PK sampling (Part C Lead-in cohorts only)				X	X	X	X	X	X		X	X	X		X					See Attachment 4 for timing of samples.

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Extension period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14[i,k]**	**15**	**22**	**1[i]**	**14[i,k]**				
PK sampling (Part C expansion phase only)				X		X	X	X			X				X					See Attachment 4 for timing of samples.
Serum markers (AFP, AFP L3, E-cadherin, PIVKA II)		X		X		X					X	X			X	X	AFP only	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period.
Immunopheno-type				X							X				X			X		Optional during the extension period (including extension period V801).
TGF-β+PF4		X		X		X					X	X			X	X		X		Optional during the extension period (including extension period V801).
MAP Panel		X				X						X				X		X		Optional during the extension period (including extension period V801).
Fibrotest		X				X						X				X				
aPTT/PT/ INR		X		X							X				X		X			Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period.

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Exten-sion Period	Visit 801	Follow - up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14[i,k]**	**15**	**22**	**1[i]**	**14[i,k]**				
Patient-Reported Outcomes																				
FACT-Hep		X									X				X			X		Optional during the extension period (including extension period V801).
Translational Research																				
Whole blood for PGx		X																		
Obtain diagnostic tumor tissue		X																		
Optional tumor biopsy	X											X								+/- 3 days after end of treatment with LY2157299

Abbreviations: AFP = alpha-fetoprotein; aPTT = activated partial prothrombin time; C = cycle; CLIP = Cancer of the Liver Italian Program; CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; FACT = Functional Assessment of Cancer Therapy; INR = international normalized ratio; MAP = multi-analyte panel; MRI = magnetic resonance imaging; PGx = pharmacogenomics; PIVKA II = prothrombin induced by vitamin K absence; PK = pharmacokinetic; PT = prothrombin time; RT-PCR = reverse transcriptase-polymerase chain reaction; TGF-β = transforming growth factor beta.

a If drug-related toxicity is present 30 days after last cycle of study drug, patients must be followed up approximately every 30 days until toxicity resolution, stabilization, another therapy is initiated, or death.

b If the patient has clinically significant cardiac findings at discontinuation (V801), echocardiography with Doppler and ECG and ECG chemistry will be repeated every 2 months for 6 months (V803, 804 and V805). If there are no cardiac findings at discontinuation (V801), 1 more echocardiography with Doppler, ECG, and ECG chemistry will be performed after 2 months (V802) unless a patient is receiving another treatment (see Section 10.2.4).

c If there were no clinically significant findings at the last assessment conducted within the 30 days following discontinuation and the patient has started another treatment, Visit 801 CT scan or chest MRI with contrast will not be performed.

d Repeat radiological scans at study discontinuation may be omitted if a patient has objective disease progression or if imaging has been performed in the previous 3 to 6 weeks.

e For details, see Attachment 4.

f Follow-up consists of Visit 802 and all subsequent visits (60 days ±7 days). For the patients in the extension phase, long-term follow up will not be conducted unless there are cardiac toxicities (Section 10.2.4).

g Echocardiography with Doppler can be performed up to 3 days prior to Day 1.
h Child-Pugh, BCLC, and CLIP assessment procedures can be found in Attachment 5, Attachment 6, and Attachment 7, respectively.
i To be performed predose LY2157299 or sorafenib.
j A delay at the start of a cycle (Day 1) of no more than 3 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not counted as a protocol violation.
k In extenuating circumstances, the "on study drug" window for LY2157299 is allowable from Day 10 to Day 14.
l Patients on study for more than 1 year (before entering extension phase) only need tests to be performed on Day 1 of each cycle.

Part D

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Extension Period	Visit 801	Follow -Up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14[i,k]**	**15**	**22**	**1[i]**	**14[i,k]**				
Procedures																				
Informed consent	X																			Informed consent must be signed prior to performing any study procedures
Medical history		X																		
Child-Pugh, Barcelona Clinic Liver Cancer (BCLC), and CLIP staging			X[h]																	
Pregnancy test			X																	
Physical exam		X		X		X					X	X			X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period
Vital signs (heart rate, blood pressure)		X		X		X					X	X			X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period
CTCAE grading		X		X		X					X	X			X		X	X	X[a]	Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period
DLT assessment										X										
Concomitant medications		X		X							X				X		X	X	X	Perform predose on Day 1 of each cycle in extension period

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Extension Period	Visit 801	Follow-Up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14[i,k]**	**15**	**22**	**1[i]**	**14[i,k]**				
Performance status		X		X		X					X	X			X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period
Tumor assessment, physical (palpable or visible)		X		X							X				X			X		Optional during the extension period (including extension period V801)
Imaging Procedures																				
Echocardiography with Doppler[g]	X										X				X		X	X[b]	X[b]	Cycles 2, 3, 4, and every other cycle (C6, C8…etc). Perform predose on Day 1 of each cycle in extension period
Chest CT scan or chest MRI		X															X	X[c]		CT scan or MRI every 6 months
Tumor assessment, radiological		X										X			X			X[d]	X[d]	Tumor assessment every 6 weeks starting Cycle 2, Day 14. May be performed 3 days around the scheduled date. Optional during the extension period (including extension period V801)
ECG		X									X				X		X	X[b]	X[b]	Cycles 2, 3, 4, and every other cycle (C6, C8,…etc). Perform predose on Day 1 of each cycle in extension period
Optional PET scan																				At discretion of the investigator

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Extension Period	Visit 801	Follow-Up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14[i,k]**	**15**	**22**	**1[i]**	**14[i,k]**				
Laboratory /Diagnostic Tests																				
ECG chemistry		X									X				X		X	X[b]	X[b]	Cycles 2, 3, 4, and every other cycle (C6, C8,…etc). Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Special chemistry			X		X	X		X			X	X		X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Hematology			X		X	X		X			X	X		X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Serum chemistry			X		X	X		X			X	X		X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Urinalysis		X[m]									X				X			X		Optional during the extension period (including extension period V801)
Urine C-terminal telopeptides of Type 1 collagen		X									X				X					Optional during the extension period
PK sampling				X		X	X				X	X	X		X					See Attachment 4 for timing of samples

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Extension Period	Visit 801	Follow-Up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14[i,k]**	**15**	**22**	**1[i]**	**14[i,k]**				
Serum markers (AFP, AFP L3, E-cadherin, PIVKA II)		X		X		X					X	X			X	X	AFP only	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Immunopheno-type				X							X				X			X		Optional during the extension period (including extension period V801)
TGF-β+PF4		X		X		X					X	X			X	X		X		Optional during the extension period (including extension period V801)
MAP panel		X				X						X				X		X		Optional during the extension period (including extension period V801)
Fibrotest		X				X						X				X				
aPTT/PT/ INR		X		X							X				X		X			Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period

Cycle/Visit[j]	Prestudy			Cycle 1							Cycle 2				Cycle 3, n[l]		Exten-sion Period	Visit 801	Follow -Up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**15**	**22**	**23**	**27**	**1[i]**	**14i,k**	**15**	**22**	**1[i]**	**14i,k**				
Patient-Reported Outcomes																				
FACT-Hep		X									X				X			X		Optional during the extension period (including extension period V801)
Translational Research																				
Whole blood for PGx		X																		
Obtain diagnostic tumor tissue		X																		
Optional tumor biopsy	X											X								+/- 3 days after end of treatment with LY2157299

Abbreviations: AFP = alpha-fetoprotein; aPTT = activated partial prothrombin time; C = cycle; CLIP = Cancer of the Liver Italian Program; CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; ECG = electrocardiogram; exam = examination; FACT = Functional Assessment of Cancer Therapy; INR = international normalized ratio; labs = laboratories; MAP = multi-analyte panel; MRI = magnetic resonance imaging; PET = positron emission tomography; PGx = pharmacogenomics; PIVKA II = prothrombin induced by vitamin K absence; PK = pharmacokinetic; PT = prothrombin time; TGF-β = transforming growth factor beta; V = visit.

a If drug-related toxicity is present 30 days after the last cycle of study drug, patients must be followed up with approximately every 30 days until toxicity resolution, stabilization, initiation of another therapy, or death.

b If the patient has clinically significant cardiac findings at discontinuation (V801), echocardiography with Doppler, ECG, and ECG chemistry will be repeated every 2 months for 6 months (V803, V804, and V805). If there are no cardiac findings at discontinuation (V801), 1 more echocardiography with Doppler, ECG, and ECG chemistry will be performed after 2 months (V802) unless a patient is receiving another treatment (see Section 10.2.4).

c If there were no clinically significant findings at the last assessment conducted within the 30 days following discontinuation and the patient has started another treatment, Visit 801 CT scan or chest MRI with contrast will not be performed.

d Repeat radiological scans at study discontinuation may be omitted if a patient has objective disease progression or if imaging has been performed in the previous 3 to 6 weeks.

e For details, see Attachment 4.

f Follow-up consists of Visit 802 and all subsequent visits (60 days ±7 days). For the patients in the extension phase, long-term follow-up will not be conducted unless there are cardiac toxicities (Section 10.2.4).

g Echocardiography with Doppler can be performed up to 3 days prior to Day 1.
h Child-Pugh, Barcelona Clinic Liver Classification, and CLIP assessment procedures can be found in Attachment 5, Attachment 6, and Attachment 7, respectively.
i To be performed predose LY2157299 or ramucirumab.
j A delay at the start of a cycle (Day 1) of no more than 3 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not counted as a protocol violation.
k In extenuating circumstances, the “on study drug” window for LY2157299 is allowable from Day 10 to Day 14.
l Patients on study for more than 1 year (before entering extension phase) only need tests to be performed on Day 1 of each cycle.
m Patient will be excluded from the study if the patient's urinary protein is >1+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates ≥2+ proteinuria, then a 24-hour urine must be collected and must demonstrate <1000 mg of protein in 24 hours to allow participation in the study.

Part E

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**21**	**22**	**1[i]**	**14[i,k]**	**1[i]**	**14[i,k]**				
Procedures																
Informed Consent	X															Informed consent must be signed prior to performing any study procedures.
Medical History		X														
Child-Pugh, Barcelona Clinic Liver Cancer (BCLC), and CLIP staging			X[h]													
Pregnancy Test			X													
Physical Exam		X		X		X			X	X	X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
Vital Signs (heart rate, blood pressure)		X		X		X			X	X	X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
CTCAE Grading		X		X		X			X	X	X		X	X	X[a]	Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
DLT Assessment								X								
Concomitant Medications		X		X					X		X		X	X	X	Perform predose on Day 1 of each cycle in extension period.
Performance Status		X		X		X			X	X	X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**21**	**22**	**1[i]**	**14[i,k]**	**1[i]**	**14i,k**				
Tumor Assessment, Physical (Palpable or Visible)		X		X					X		X			X		Optional during the extension period (including extension period V801)
Imaging Procedures																
Echocardiogram with Doppler[g]	X								X		X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8, etc). Perform predose on Day 1 of each cycle in extension period
Chest CT Scan or Chest MRI		X											X	X[c]		CT scan or MRI every 6 months
Tumor Assessment, Radiological		X								X	X			X[d]	X[d]	Tumor assessment every 6 weeks starting Cycle 2, Day 14. May be performed 3 days around the scheduled date. Optional during the extension period (including extension period V801)
ECG		X							X		X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8, etc). Perform predose on Day 1 of each cycle in extension period

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**21**	**22**	**1[i]**	**14[i, k]**	**1[i]**	**14[i, k]**				
Laboratory /Diagnostic Tests																
ECG chemistry		X							X		X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8, etc). Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Special chemistry			X		X	X		X	X	X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Hematology			X		X	X		X	X	X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Serum chemistry			X		X	X		X	X	X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Urinalysis		X							X		X			X		Optional during the extension period (including extension period V801)
Urine C-terminal telopeptides of Type 1 collagen		X							X		X					Optional during the extension period

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	21	**22**	**1[i]**	**14[i,k]**	**1[i]**	**14[i,k]**				
PK sampling[e]				X			X	X	X		X					Timed with ECG. See Attachment 4 for specific timepoints.
Serum markers (AFP, AFP L3, E-cadherin, PIVKA II)		X		X			X		X		X		AFP only	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Immuno-phenotype				X					X		X			X		Optional during the extension period (including extension period V801)
TGF-β+PF4		X		X			X		X		X			X		Optional during the extension period (including extension period V801)
MAP panel				X			X		X		X			X		Optional during the extension period (including extension period V801)
Fibrotest		X					X		X		X					
aPTT/PT/ INR		X		X					X		X		X			Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Patient-Reported Outcomes																
FACT-Hep		X							X		X			X		Optional during the extension period (including extension period V801)

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤ 7**	**1[i]**	**8[i]**	**14[i]**	**21**	**22**	**1[i]**	**14[i,k]**	**1[i]**	**14[i,k]**				
Translational Research																
Whole blood for PGx		X														
Obtained diagnostic tumor tissue, when available		X														
Optional tumor biopsy	X									X						+/- 3 days after end of treatment with LY2157299

Abbreviations: AFP = alpha-fetoprotein; aPTT = activated partial prothrombin time; C = cycle; CLIP = Cancer of the Liver Italian Program; CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; FACT = Functional Assessment of Cancer Therapy; INR = international normalized ratio; MAP = multi-analyte panel; MRI = magnetic resonance imaging; PGx = pharmacogenomics; PIVKA II = prothrombin induced by vitamin K absence; PK = pharmacokinetic; PT = prothrombin time; TGF-β = transforming growth factor beta.

a If drug-related toxicity is present 30 days after last cycle of study drug, patients must be followed up approximately every 30 days until toxicity resolution, stabilization, another therapy is initiated, or death.

b If the patient has clinically significant cardiac findings at discontinuation (V801), echocardiography with Doppler, ECG, and ECG chemistry will be repeated every 2 months for 6 months (V803, V804, and V805). If there are no cardiac findings at discontinuation (V801), 1 more echocardiography with Doppler, ECG, and ECG chemistry will be performed after 2 months (V802) unless a patient is receiving another treatment (see Section 10.2.4).

c If there were no clinically significant findings at the last assessment conducted within the 30 days following discontinuation and the patient has started another treatment, Visit 801 CT scan or chest MRI with contrast will not be performed.

d Repeat radiological scans at study discontinuation may be omitted if a patient has objective disease progression or if imaging has been performed in the previous 3 to 6 weeks.

e For details, see Attachment 4. PK sampling will be performed on Cycle 1, with a predose sample on Day 1 of Cycle 2 and all subsequent cycles.

f Follow-up consists of Visit 802 and all subsequent visits (60 days ±7 days). All patients will be followed for OS until study completion.

g Echocardiogram with Doppler can be performed up to 3 days prior to Day 1.

h Child-Pugh, BCLC, and CLIP assessment procedures can be found in Attachment 5, Attachment 6, and Attachment 7, respectively.

i To be performed predose LY2157299.

j A delay at the start of a cycle (Day 1) of no more than 3 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not counted as a protocol violation.

k In extenuating circumstances, the ‘on study drug’ window is allowable from Day 10 to Day 14.
l Patients on study for more than 1 year (before entering extension phase) only need tests to be performed on Day 1 of each cycle.

Attachment 2. Protocol JBAK Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[b]
Hemoglobin	Total bilirubin
Erythrocyte count (RBC)	Direct bilirubin
Leukocytes (WBC)	Total Protein
Neutrophils, segmented + bands	Alkaline phosphatase
Lymphocytes	LDH
Monocytes	Creatinine kinase (CK)
Eosinophils	ALT/SGPT
Basophils	AST/SGOT
Platelets	Blood urea nitrogen (BUN)
	Creatinine
Immunophenotype[b]	Uric acid
	Calcium
Urinalysis[a]	Glucose, random (nonfasting)
Specific gravity	Albumin
pH	Cholesterol
Protein	Phosphorus
Glucose	Sodium
Ketones	Potassium
Blood	Magnesium
Leukocyte esterase	
	AFP[b]
ECG Chemistry[b]	AFP L3[b]
Lipase	PIVKA II[b]
Thyroid Stimulating Hormone (TSH)	E-cadherin[b]
Tri-iodothyronine (T3)	TGF-β+PF4[b]
Thyroxine (T4)	
Calcium[c]	aPPT/PT/INR[b]
Glucose, random (nonfasting) [c]	
Albumin[c]	Fibrotest[b]
Phosphorus[c]	
Sodium[c]	Urine C-terminal telopeptides of Type 1 Collagen[b]
Potassium[c]	
Magnesium[c]	Serum Pregnancy Test (females only)[a]
Special Chemistry[b]	
Cystatin C	
Troponin I	
BNP	
High-sensitivity C-reactive protein (hs-CRP)	

Abbreviations: AFP = alpha-fetoprotein; ALT = alanine aminotransaminase; aPTT = activated partial prothrombin time; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; ECG = electrocardiogram; INR = international normalized ratio; LDH = Lactate Dehydrogenase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells; PIVKA II = prothrombin induced by vitamin K absence.

[a] All samples will be discarded within 60 days of validated test results. Validation will occur at the time of initial testing. All these tests will be performed at a local or investigator-designated laboratory, with the exception of immunophenotype.

[b] All samples will be discarded within 60 days of validated test results. Validation will occur at the time of initial testing. All these tests will be performed at a Lilly-designated laboratory. Tests will be performed at a local laboratory if performed during the treatment extension period.

[c] Test not performed if both chemistry and ECG chemistry are required. See Attachment 1.

Attachment 3. Protocol JBAK ECOG Performance Status

ECOG Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. *Am J Clin Oncol.* 1982;Dec;5(6):649-655.

Attachment 4. Protocol JBAK Pharmacokinetic Sampling Instructions

Sparse PK Sampling Schedule Parts A and B

Sample Number	Cycle	Day	Sampling Windows for PK
1	1	1	Predose[a]
2	1	1	0.5-2 hours
3	1	14	Predose[a]
4	1	14	0.5-2 hours
5[b]	1	14	3-5 hours
6[b]	1	15	Morning
7	1	22	Morning
8	2	1	Predose[a]
9	3, n	1	Predose[a]

Abbreviations: n = cycle number ≥Cycle 4; PK = pharmacokinetic.

[a] The predose sample has to be taken before receiving any LY2157299.

[b] For patients who will have a Day 15 PK sample taken, their evening dose of LY2157299 on Day 14 should be omitted.

Part C Sampling Schedule for Safety Lead-in Cohorts

Day	LY2157299 + Sorafenib Dosing Schedule	Sampling Times	
		Pharmacokinetics (LY2157299)	**Pharmacokinetics (Sorafenib)**
Cycle 1 Day 1 (Day at which sorafenib and LY2157299 are combined)	Both drugs as per Section 9	Predose[a]	Predose[a]
		0.5 h after dose	0.5 h after dose
		2 h after dose	2 h after dose
		3 h after dose	3 h after dose
		6 h after dose	6 h after dose
Cycle 1 Day 8	Both drugs as per Section 9	Predose[a]	Predose[a]
Cycle 1 Day 14[b] (last day of LY2157299 dosing)	Both drugs as per Section 9	Predose[a]	Predose[a]
		0.5 h after dose	0.5 h after dose
		2 h after dose	2 h after dose
		3 h after dose	3 h after dose
		6 h after dose	6 h after dose
Cycle 1 Day 15[b]	Sorafenib only as per Section 9	Morning (before sorafenib is taken)	Morning (before sorafenib is taken)
Cycle 1 Day 22	Sorafenib only as per Section 9		Predose[a]
			0.5 h after dose
			2 h after dose
			3 h after dose
			6 h after dose
Cycle 1 Day 23	Sorafenib only as per Section 9		Morning PK (predose)
Cycle 2 Day 1	Both drugs as per Section 9	Predose[a]	Predose[a]
Cycle 2 Day 1	Both drugs as per Section 9	0.5-2 hours	0.5-2 h
Cycle 2, Day 14[b]	Both drugs as per Section 9	Predose[a]	Predose[a]
Cycle 2, Day 14[b]	Both drugs as per Section 9	0.5-2 hours	0.5-2 h
Cycle 2, Day 14[b]	Both drugs as per Section 9	3-5 hours	3-5 h
Cycle 2, Day 15[b]	Sorafenib only as per Section 9	Morning (before sorafenib is taken)	Predose[a]
Cycle 3, Day 1	Both drugs as per Section 9	Predose[a]	Predose[a]
Cycle 4, n, Day 1	Both drugs as per Section 9	Predose[a]	Predose[a]

Abbreviations: h = hour(s); n = cycle number ≥Cycle 4; PK = pharmacokinetic.

a The predose sample has to be taken before receiving any LY2157299 or sorafenib.

b For patients who will have a Day 15 PK sample taken, their evening dose of LY2157299 on Day 14 should be omitted.

Part C Sampling Schedule for LY2157299 and Sorafenib in Expansion Cohort

Sample Number	Cycle	Day	Sampling Windows for PK
1	1	1	Predose[a]
2	1	1	0.5-2 hours
3	1	14	Predose[a]
4	1	14	0.5-2 hours
5[b]	1	14	3-5 hours
6[b]	1	15	Morning
7	1	22	Morning
8	2	1	Predose[a]
9	3, n	1	Predose[a]

Abbreviation: PK = pharmacokinetic.

a The predose sample has to be taken before receiving any LY2157299 or sorafenib.

b For patients who will have a Day 15 PK sample taken, their evening dose of LY2157299 on Day 14 should be omitted.

Part D Sampling Schedule

Day	LY2157299 + RAM Dosing Schedule	Pharmacokinetic Sampling Times (LY2157299) plasma	Pharmacokinetic Sampling Times (RAM) serum
Cycle 1 Day 1 (Day at which RAM and LY2157299 are combined)	Both drugs as per Section 9	Predose[a]	Predose[a]
		1.5-3 h after LY2157299 dose	End of RAM infusion
Cycle 1 Day 14[b] (last day of LY2157299 dosing)	LY2157299 as per Section 9	Predose[a]	
		0.5 h after dose	
		2 h after dose	
		3 h after dose	
		6 h after dose	
Cycle 1 Day 15[b]	RAM only as per Section 9	Morning (before RAM is taken)	Predose
Cycle 1 Day 15	RAM only as per Section 9		End of RAM infusion
Cycle 2 Day 1	Both drugs as per Section 9	Predose[a]	Predose[a]
		1.5-3 hours after dose (LY)	End of RAM infusion
Cycle 2, Day 14[b]	LY2157299 as per Section 9	Predose[a]	
		0.5-2 hours	
		3-5 hours	
Cycle 2, Day 15[b]	RAM only as per Section 9	Morning (before RAM is taken)	Predose
Cycle 2 Day 15	RAM only as per Section 9		End of RAM infusion
Cycle 3, Day 1	Both drugs as per Section 9	Predose[a]	Predose[a]
Cycle 4, n, Day 1	Both drugs as per Section 9	Predose[a]	Predose[a]

Abbreviations: h = hour(s); LY = LY2157299; n = cycle number ≥Cycle 4; PK = pharmacokinetic; RAM = ramucirumab.

a The predose sample has to be taken before receiving any LY2157299 or ramucirumab.

b For patients who will have a Day 15 PK sample taken, their evening dose of LY2157299 on Day 14 should be omitted.

Part E Sampling Schedule for LY2157299

Sample Number	Cycle	Day	Sampling Windows for PK
1	1	1	Predose[a]
2	1	1	0.5-2 hours
3	1	21	Predose[a]
4	1	21	0.5-2 hours
5[b]	1	21	3-5 hours
6[b]	1	22	Morning
7	2	1	Predose[a]
8	3 - n	1	Predose[a]

Abbreviation: PK = pharmacokinetic.

a The predose sample should be taken before the patient receives any LY2157299.

b For patients who will have a Day 22 PK sample taken, the evening dose of LY2157299 on Day 21 should be omitted.

Attachment 5. Protocol JBAK Child-Pugh Score

Child-Pugh Score

Clinical and biochemical parameters	Points		
	1	**2**	**3**
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL	>3.5	2.8-3.5	<2.8
Ascites	Absent	Moderate	Tense
Encephalopathy	Absent	Moderate (Stage I-II)	Severe (Stage III-IV)
Prothrombin time			
Sec prolonged	<4	4-6	>6
%	>60	40-60	<40
INR[a]	<1.7	1.7-2.3	>2.3
In case of primary biliary cirrhosis			
	1	**2**	**3**
Bilirubin (mg/dL)	<4	4-10	>10

Total points:

- 5 to 6: Child-Pugh class A
- 7 to 9: Child-Pugh class B
- 10 to 15: Child-Pugh class C

[a] INR (International Normalized Ratio) is an expression of prothrombin time, corrected by the sensitivity of the reactive to anticoagulants and should be validated as an alternative to prothrombin time in liver insufficiency.

Source: Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-649.

Attachment 6. Protocol JBAK Barcelona Clinic Liver Cancer Classification Table

Barcelona Clinic Liver Classification Table

Stage	Performance Status Test	Tumor Stage	Okuda Stage	Liver Function Status
A	0	Single	I-II	Child-Pugh A-B
B	0	Large multinodular	I-II	Child-Pugh A-B
C	1-2	Vascular invasion/ extrahepatic spread	I-II	Child-Pugh A-B
D	3-4	Any	III	Child-Pugh C

Note: Stages A and B, all criteria should be fulfilled; Stages C and D, at least 1 criterion.

Source: Llovet JM, Burroughs A, Bruix J. Hepatocellular Carcinoma. *Lancet*. 2003;362:1907.

Attachment 7. Protocol JBAK Cancer of the Liver Italian Program (CLIP) Scoring System

CLIP Scoring System

Variable	Score
Child-Pugh stage	
A	0
B	1
C	2
Tumor morphology	
Uninodular and extension ≤50%	0
Multinodular and extension ≤50%	1
Massive or extension >50%	2
AFP	
<400	0
≥400	1
Portal vein thrombosis	
No	0
Yes	1

Abbreviation: AFP = alpha-fetoprotein.
Source: The Cancer of the Liver Italian Program (CLIP) Investigators. *Hepatology*. 2000;31(4):840-845.

Attachment 8. Protocol JBAK 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).

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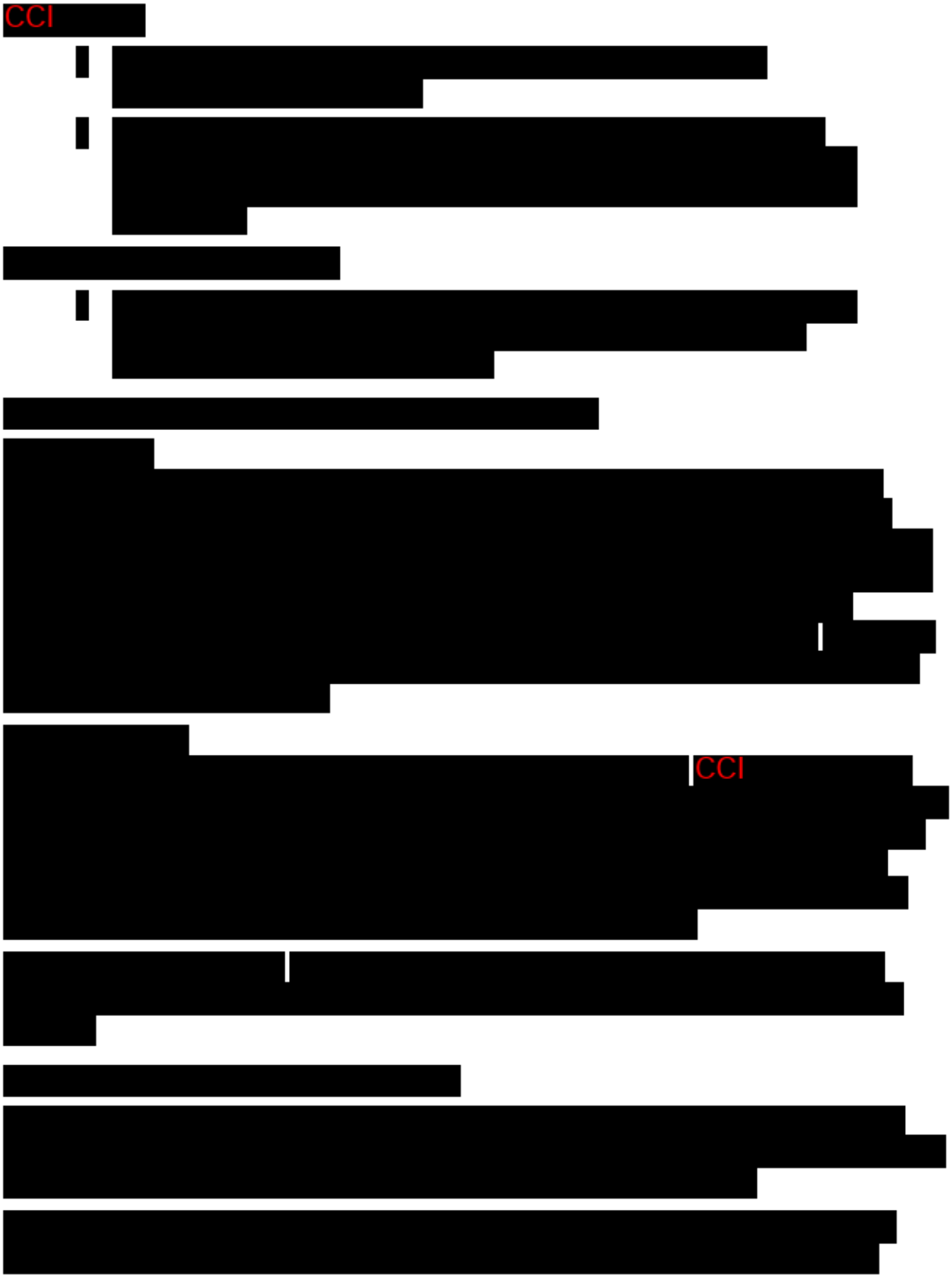
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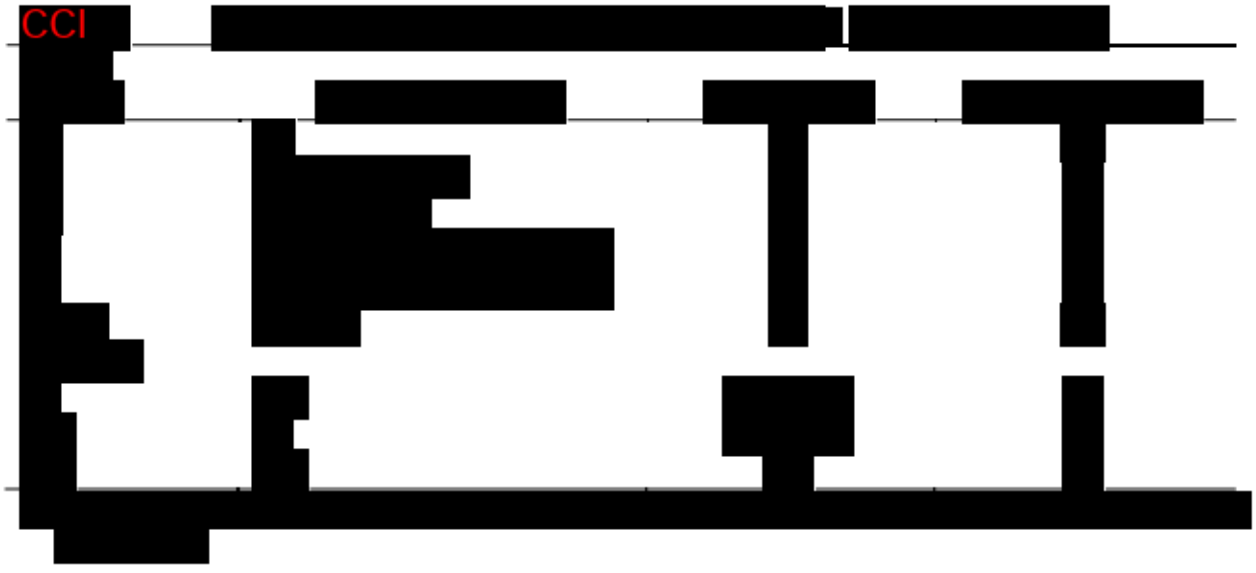

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Attachment 9. Protocol JBAK Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

-OR-

$$\text{GFR (mL/min/1.73 m}^2) = 170 \times [\text{PCr}]^{-0.999} \times [\text{age}]^{-0.176}$$

$$\times [0.762 \text{ if patient is female}] \times [1.18 \text{ if patient is black}]$$

$$\times [\text{SUN}]^{-0.17} \times [\text{Alb}]^{+0.318}$$

Abbreviations: PCr= plasma creatinine, mg/dL; SUN= serum urea nitrogen, mg/dL; Alb= serum albumin, g/dL

Source: Murray PT, Ratain MJ. Estimation of the glomerular filtration rate in cancer patients: a new formula for new drugs. *J Clin Oncol*. 2003;21:2664-2672.

Attachment 10. Protocol JBAK FACT-Hep

The FACT-Hep assesses additional concerns for hepatobiliary (liver, bile duct, and pancreas) cancer patients. Score calculations are based on the FACT-Hep scoring guidelines in Section 3 of the manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Scales, Version 4.

FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

Attachment 11. Protocol JBAK New York Heart Association Functional Classification

The New York Heart Association Functional Classification classifies the extent of heart failure by placing patients in 1 of 4 categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain:

Class I: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Reference

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little, Brown & Co; 1994.

Attachment 12. Protocol JBAK Echocardiography

Echocardiography

In this study, echocardiographic images are acquired with the purpose of ascertaining that patients enrolled in the study have baseline (and maintain during the study) normal cardiac structure and function, normal pulmonary artery pressure and absence of significant valvular disease (defined herein as no valvular regurgitation except for mild tricuspid, mild mitral, mild aortic regurgitation, and no more than mild mitral or aortic valvular stenosis). Repeated echocardiograms in each subject are performed to establish the cardiac safety of LY2157299 by comparison with the initial studies. Determination of normalcy status requires objective evaluation of cardiac chamber size and function and attention to the use of appropriate techniques in the performance of the echocardiographic examinations, in particular the use of standardized settings during the acquisitions of color-flow Doppler imaging. Therefore, because quantitative echocardiography is the goal, stringent criteria for image quality and reproducibility are essential.

In addition to qualitative assessment of valvular regurgitation when or if detected (trace, mild, moderate, or severe according to Singh et al. 1999 and Zoghbi et al. 2003 (see below) and qualitative/quantitative assessment of valvular stenosis when or if detected (mild, moderate or severe, using mean and peak pressure gradient in mm Hg and orifice area in cm^2 as applicable), other echocardiographic parameters to be serially quantified are left ventricular (LV) cavity size (diameters, volumes; assisted by IV injection of left-sided contrast echocardiographic agents). LV ejection fraction (EF), LV mass and mass index, diastolic function based on mitral flow velocity, mitral deceleration time, pulmonary venous flow pattern, tissue Doppler, extrapolation of LV end-diastolic pressure by E/Em, left atrial (LA) volume index, and extrapolation of pulmonary artery systolic pressure based on contrast-enhanced tricuspid regurgitation Doppler data.

An echocardiogram with no clinically significant abnormalities is one defined specifically as the LV internal dimension in diastole should be $\leq$2.8 cm/M^2 (Schiller et al. 1989) the LA end-systolic volume should be $\leq$36 mL/M^2 (Tsang et al. 2002), the LVEF should be $\geq$50% without regional wall motion abnormalities (Oh), 2-dimensional echocardiographic-derived LV mass index should be $\leq$115 g/M^2 for males and $\leq$99 g/M^2 for females (Schiller et al. 1989), the pulmonary artery pressure should be normal (tricuspid regurgitation jet velocity $\leq$2.5 ms and/or pulmonary valve flow acceleration time $\geq$120 ms), the LV diastolic function should be normal (screening: mitral deceleration time $\geq$150 ms and $\leq$250 ms, mitral E/A ratio $\geq$0.75 and $\leq$1.5, mitral E velocity divided by Doppler mitral annular velocity [E/Em] <15) (Khouri et al. 2004), and there should be no evidence for pericardial or congenital or heart disease. In addition, there should be no evidence for more than mild mitral or aortic stenosis (mitral valve area should be greater than 2 cm^2, and aortic valve area should be >1.5 cm^2), no evidence of more than mild mitral or aortic regurgitation (Singh et al. 1999 and Zoghbi et al. 2003). Patients enrolled in the

study may have evidence for tricuspid (trace or mild), pulmonary, mitral (trace or mild) or aortic (trace or mild) regurgitation by Doppler techniques (Singh et al. 1999 and Zoghbi et al. 2003).

References

Khouri SJ, Maly GT, Suh DD, Walsh TE. A practical approach to the echocardiographic evaluation of diastolic function. *J Am Soc Echocardiogr.* 2004;17:290-297.

Oh JK. The Echo Manual, 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2006.

Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Reicheck N, Sahn D, Schnittger I, Silverman NH, Tajik AJ. Recommendations for quantitation of the left ventricle by two dimensional echocardiography. *J Am Soc Echocardiogr*. 1989;2:358-367.

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study). *Am J Cardiol.* 1999;83:897-902.

Tsang TSM, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol*. 2002;90:1284-1289.

Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777-802.

Echocardiographic Certification Process

To ensure protocol adherence, each study center will be required to submit an initial study for certification. The certification study will be performed on the first patient at the study site. Once a certification certificate is received from Biomedical Systems the site may begin seeing additional study patients.

General Instructions for Echocardiography

- Allow 1 hour for the performance of the echocardiographic examination in each patient.
- Do not enter the patient's name in the initial video screen of the echocardiographic imaging system or protocol. Only the patient's screen and/or randomization number is to be entered and visible during the echocardiogram recording.

- Set the echocardiography imaging system (create preset "Lilly" and use in subsequent visits of patients in the study) to acquire and store digital 3 cardiac cycles loops for 2-dimensional echocardiographic image per screen and obtain at least 3 or more cardiac cycles per each M-Mode or Doppler spectral-image screen.
- This protocol calls for the use of both, harmonic imaging (for all views; native or tissue harmonics, using high [>1.3] mechanical index, with the appropriate highest transmitted frequency possible for that transducer) as well as fundamental imaging (this for limited views of the aortic and mitral valve on parasternal long axis).
- Obtain the patient's height and weight at the time of the examination and include with the study data.
- Obtain and record with the study data the patient's arterial blood pressure in right arm while undergoing echocardiography in the recumbent left-lateral position.
- Display the electrocardiogram (ECG) at all times during echocardiographic sequence recordings.
- Obtain all image sequences at held expiration (for up to 5 seconds at a time).
- Record images (2D and color-flow Doppler cine loops, frames for M-Mode and Doppler spectral) in digital form and copy to a CD-ROM or MO-disk for each patient per visit.
- Choose the best transmit gain, TGCs, mechanical index and compression setting for each patient. Record these settings and use them at all future visits for each specific patient.
- Always obtain all images (except subcostal) at held-end expiration with the patient lying on the left side (45 to 60 degrees) at 16-cm depth of field. In the rare instance when the apical view silhouette of the heart (including the atria) exceeds 16 cm, then employ a 20-cm depth setting and make a note of this to employ 20-cm depth for that patient in subsequent visits.
- Employ Doppler color-flow imaging from all views (long axis, short axis, apical 4-chamber, apical 2-chamber, and apical long axis) and note presence of valvular regurgitation. For Doppler color flow, employ a Nyquist limit of 50 to 60 cm/sec, and set the color gain at a level that just eliminates random color speckle from nonmoving regions. Before recording Doppler color-flow image data for the first time in each patient at each visit, record continuously in videotape while the adjustment of color gain is performed to document in the videotaped data that gain settings have been properly obtained. Avoid using very high or very low levels of pulse-repetition frequency (PRF). Also, employ a color sector or color region of interest as narrow as possible for each valve examination, and with the least depth, to maximize lateral and temporal resolution.

- Spectral Doppler and M-Mode echocardiography data are to be recorded at a display speed of 50 or 100 mm/s (use discretion considering heart rate; videotape) using optimal gain control and minimal filter setting (at least 3 beats), also at held expiration.
- Before starting the second or subsequent visit echocardiogram for a given patient:

  A. Retrieve the cine loop, from the patient's first study digital data set, 2D images of the left ventricle (short axis) as acquired in the original study.

  B. Utilize this cine loop as part of a split screen to use as a guide to obtain the same imaging plane of the short axis again for this and subsequent visits of the same patient.

After obtaining the current image, acquire a new image of both, short axis LV images

- Keep a set of the digital images of each echocardiogram obtained for that particular patient into a "master" file to remain in the site's echocardiography laboratory and send via courier mail a CD-ROM or MO-disk copy of each study to the Core Echocardiography Laboratory at Biomedical Systems, St. Louis. Use the provided preprinted shipping forms included with this manual. If additional forms are required, please contact Biomedical Systems Echocardiography Laboratory in St. Louis.

Echocardiography Protocol; Required Views

Parasternal Long-Axis View, 16-cm depth

- Record 3 beats (held expiration) of the entire 2D image with harmonic imaging.
- Employ color-flow Doppler to evaluate for aortic and mitral regurgitation (using here and at each time that color-flow Doppler is used, the procedures described above regarding Nyquist limits, gain, and PRF) and record 3 beats (held expiration).
- Obtain M-Mode views of the LV as close as possible to the minor axis of the ventricle, avoiding the papillary muscle, and obtain a freeze-frame M-Mode image (50 to 100 mm/s display).
- Switch to fundamental imaging (this is, the only sequence of the protocol that requires fundamental imaging) by turning off the harmonic imaging mode; then place a small region of 2D sector or region of interest (2D only without color flow; at >45 Hz frame rate) that includes both the aortic and mitral valve leaflets, and record 3 beats (held expiration).

Parasternal Short-Axis View, 16-cm depth

- Record 2D harmonic imaging views of the aortic, mitral valve, and papillary muscle level of the LV and record a sweep sequence of 5 beats.
- Employ color-flow Doppler to evaluate for aortic regurgitation (record 3 beats in held expiration), then for mitral regurgitation at the level of the aortic root/left atrium (record 3 beats in held expiration).
- Obtain pulsed spectral Doppler of the pulmonary valve flow at the level of the right-ventricular outflow tract; freeze and record spectral display of 3 to 5 beats at held expiration.
- If this is the second study in this patient, compare to previous image in the same patient (loop) to ensure obtaining the same LV papillary muscle level. This procedure entails retrieving from digital data of the site's laboratory master storage of the same patient's previous echocardiogram tape that contains the short-axis view
- Once it has been ascertained that the same papillary muscle level is being obtained today, as before, acquire (end-expiration) and save "today's" short axis LV papillary muscle level; record both for 3 beats.

Apical 4-Chamber View, 16- or 20-cm depth

- Avoid foreshortening of the image by maximizing the length of the LV cavity with the transducer placed as lateral and leftward as possible (toward the axilla and at a lower interspace in the left chest wall). Likewise, obtain the widest possible LV cavity to ensure optimal assessment of LV volumes.
- Pay special attention to optimal visualization of the endocardium of the lateral wall and septum and avoid visualization of the papillary muscle in this view. Record 5 beats with harmonic imaging at held expiration.
- Employ color-flow Doppler to evaluate for mitral and tricuspid regurgitation (using procedures described above for settings, etc.) and record 3 beats for each valve.
- Record at least 3 beats of the pulsed Doppler transmitral-flow velocity with the sample volume (smallest size possible) positioned both at the mitral leaflet tips and at the mitral annulus level with the left atrium; (displayed at 100 mm/s).
- Then measure the flow velocity across the mitral valve employing continuous-wave Doppler (3 beats, spectral display recording, 50 to 100 mm/s).
- Record at least 3 beats of the pulmonary venous-flow velocities (pulsed Doppler spectral) with the sample volume at the right upper pulmonary vein entrance into the left atrium.
- Record at least 3 beats of the pulsed Doppler transtricuspid-flow velocity with the sample volume positioned at the tips of the tricuspid valve.

- Then measure the flow-velocity spectra across the tricuspid valve employing continuous-wave Doppler (tricuspid-regurgitation peak-flow velocity; 3 beats, spectral display recording, 50 to 100 mm/s).
- If the tricuspid regurgitation jet is incompletely visualized or truncated (examples to be discussed and shown at investigators' meeting), this calls for the use of agitated-saline contrast echocardiography (harmonic imaging, high mechanical index) to be employed to enhance the detection of the peak velocity of the tricuspid regurgitation jet. For this purpose, start a 20-gauge or larger peripheral IV (antecubital vein preferred). Draw 9 mL of sterile saline into a 10-mL syringe, connect it to a 3-way stopcock, and connect an empty 10-mL syringe to the other port. Leave 1 mL of air in the saline syringe. Agitate the solution by rapidly transferring the volume from 1 syringe to the other. Expel all visible bubbles from the syringe that will be used for injection (for contrast, it is not necessary to inject visible air, and it is dangerous and contraindicated to do so). Before injecting, point the syringe with saline downward so any remaining visible bubbles may rise towards the plunger (away from the patient). Inject only 7 mL of the 9 mL of saline on the syringe, leaving a residual of 2 mL in that syringe. This avoids the injection of visible bubbles.
- For recording of the tricuspid regurgitation peak jet after saline enhancement, be prepared to quickly reduce the Doppler spectral gain to avoid noise-artifact blooming of the signal once the saline contrast effect is detected at the tricuspid-valve inlet. Using continuous-wave Doppler, obtain at least 3 beats with the enhanced Doppler signal; freeze the spectral display, and record for 5 seconds.
- Obtain by tissue-Doppler echocardiography (initially by real-time 2D color display to facilitate placement of the sample volume within the LV myocardium) the spectral data of myocardial velocities at the level of the mitral annulus (lateral wall or interventricular-septum site) and freeze a spectral display (50 mm/s; at least 3 to 4 beats, held end expiration) and record (apply procedures for specific manufacturers regarding presets with optimal settings for map, gain, power, dark background in the display, etc.). Ensure that the ECG is displayed above the Doppler tissue spectral data.

Apical 5-Chamber View, 16-cm depth

- Record 3 beats of the apical 5-chamber view harmonic imaging color-flow Doppler (to evaluate for aortic regurgitation).
- Place a sample volume within 1 cm of the aortic valve in the LV outflow tract and record (at held expiration) at least 3 beats of spectral-pulsed Doppler of the flow velocity in the outflow tract (displaying the closing [but not the opening] valve clicks, at 50 or 100 mm/s spectral-display speed).

- Then measure the flow velocity across the aortic valve employing continuous-wave Doppler (3 beats, spectral-display recording, 50 to 100 mm/s) displaying both systolic- and any diastolic-flow velocity spectra (held expiration).

Apical 2-Chamber View, 16- or 20-cm depth

- Obtain 3 beats at held expiration (or held inspiration, if necessary for this view only) of the harmonic imaging apical 2-chamber view. Avoid foreshortening of the view by obtaining the longest possible major-axis length displayed and the widest possible cavity.
- Employ color-flow Doppler to evaluate for mitral regurgitation and record 3 beats.

Apical Long-Axis View, 16- or 20-cm depth

- Record 3 beats of the harmonic imaging apical long-axis 2D examination employing held expiration. Again, avoid foreshortening the view by obtaining the longest as well as the widest possible LV cavity area.
- Employ color-flow Doppler to evaluate for mitral and aortic regurgitation and record 3 beats for each valve image.

Subcostal View, 20- or 24-cm depth (if necessary)

- Record 3 beats continuously with harmonic imaging of the inferior vena cava while asking the patient to abruptly sniff once.

Attachment 13. Protocol JBAK Qualitative and Quantitative Parameters for Grading Valvular Regurgitation

(Mitral and Aortic) Regurgitation Severity

Please refer to references below for information on qualitative and quantitative parameters for grading valvular (mitral and aortic) regurgitation severity.

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study). *Am J Cardiol*. 1999;83:897-902.

Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777-802.

Attachment 14. Protocol JBAK Guidance for Sorafenib Eligibility

From the UK NHS Guidance

www.medicines.org.uk/guides (Last updated 05 May 11)

Sorafenib tosylate

Sorafenib 200-mg tablets when used in liver carcinoma

Whether this medicine is suitable for you

Sorafenib tosylate is not suitable for everyone and some people should never use it. Other people should only use it with special care. It is important that the person prescribing this medicine knows your full medical history.

Your prescriber may only prescribe this medicine with special care or may not prescribe it at all if you:

- are allergic or sensitive to or have had a reaction to any of the ingredients in the medicine
- are on dialysis
- have liver problems
- have high blood pressure
- have heart problems
- have recently had a heart attack
- have or have had a stomach ulcer
- have a wound that is still healing
- are elderly
- are about to have surgery
- have metabolic problems
- have risk factors for developing kidney problems
- have taken rifampicin within the last 5 days

Furthermore the prescriber may only prescribe this medicine with special care or may not prescribe it at all for someone under the age of 18 years.

As part of the process of assessing suitability to take this medicine a prescriber may also arrange tests:

- to check that this medicine is having the desired effect
- to check that this medicine is not having any undesired effects

Over time it is possible that Sorafenib tosylate can become unsuitable for some people, or they may become unsuitable for it. If at any time it appears that Sorafenib tosylate has become unsuitable, it is important that the prescriber is contacted immediately.

Attachment 15. Modified RECIST Assessment for Hepatocellular Carcinoma

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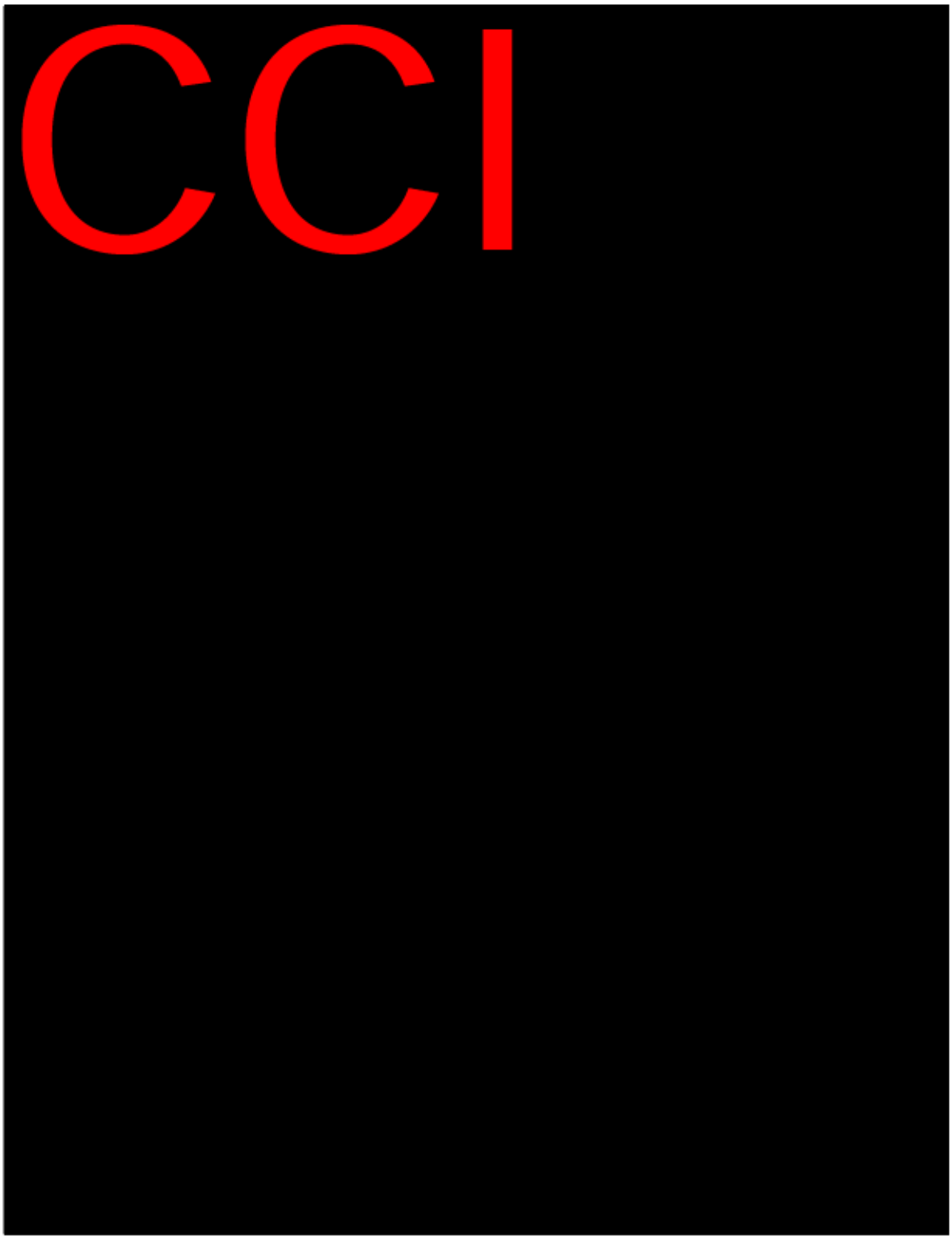
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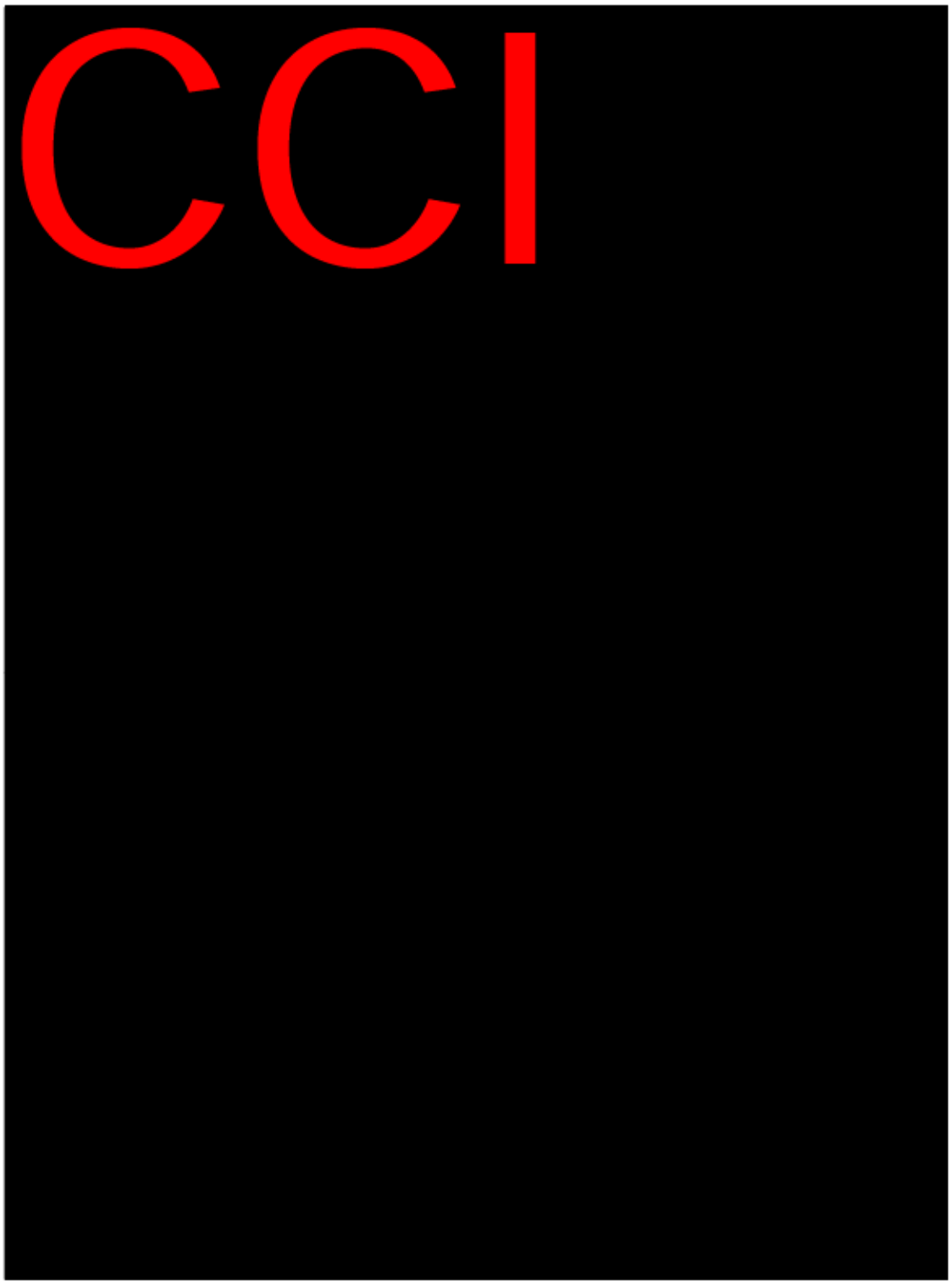
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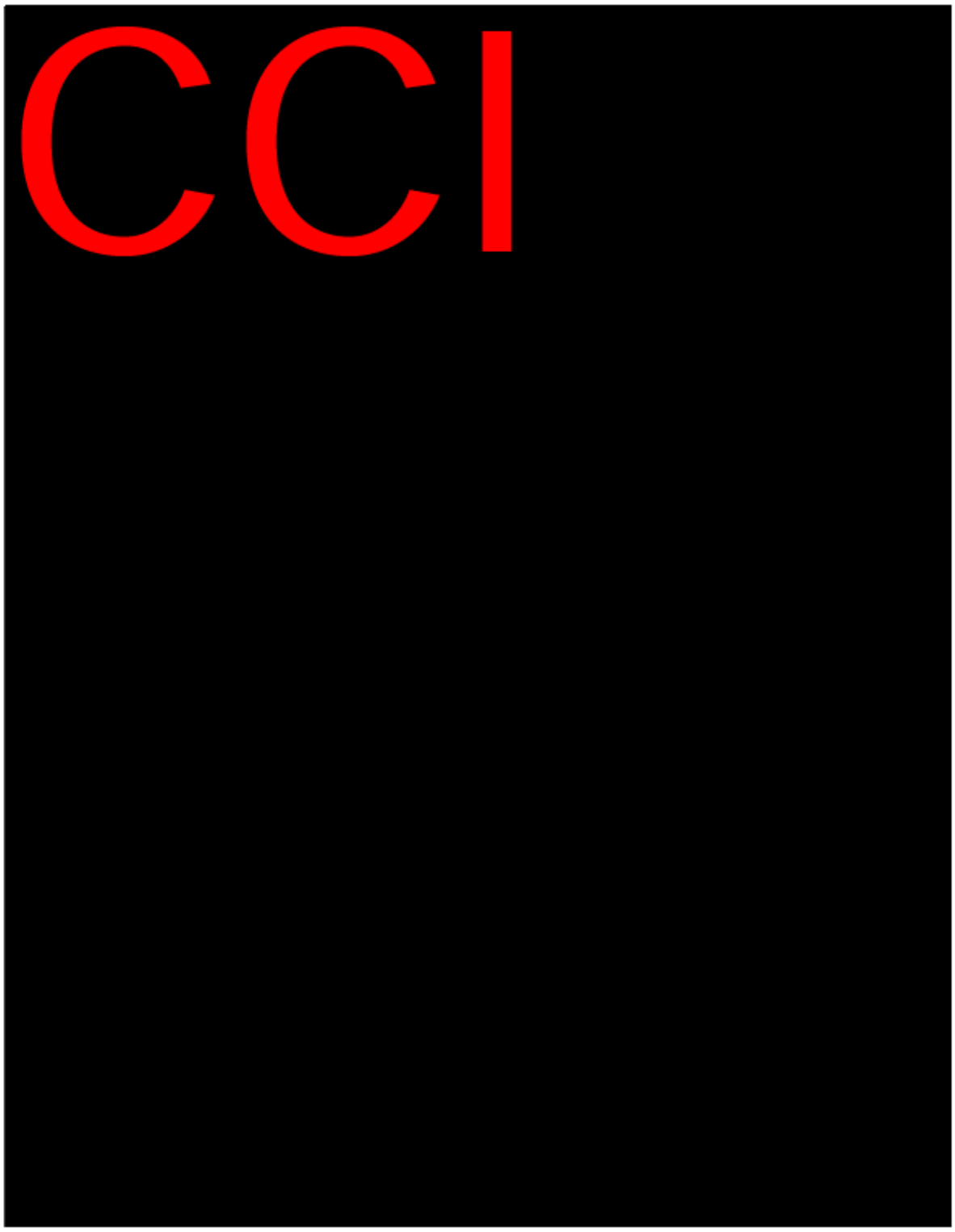
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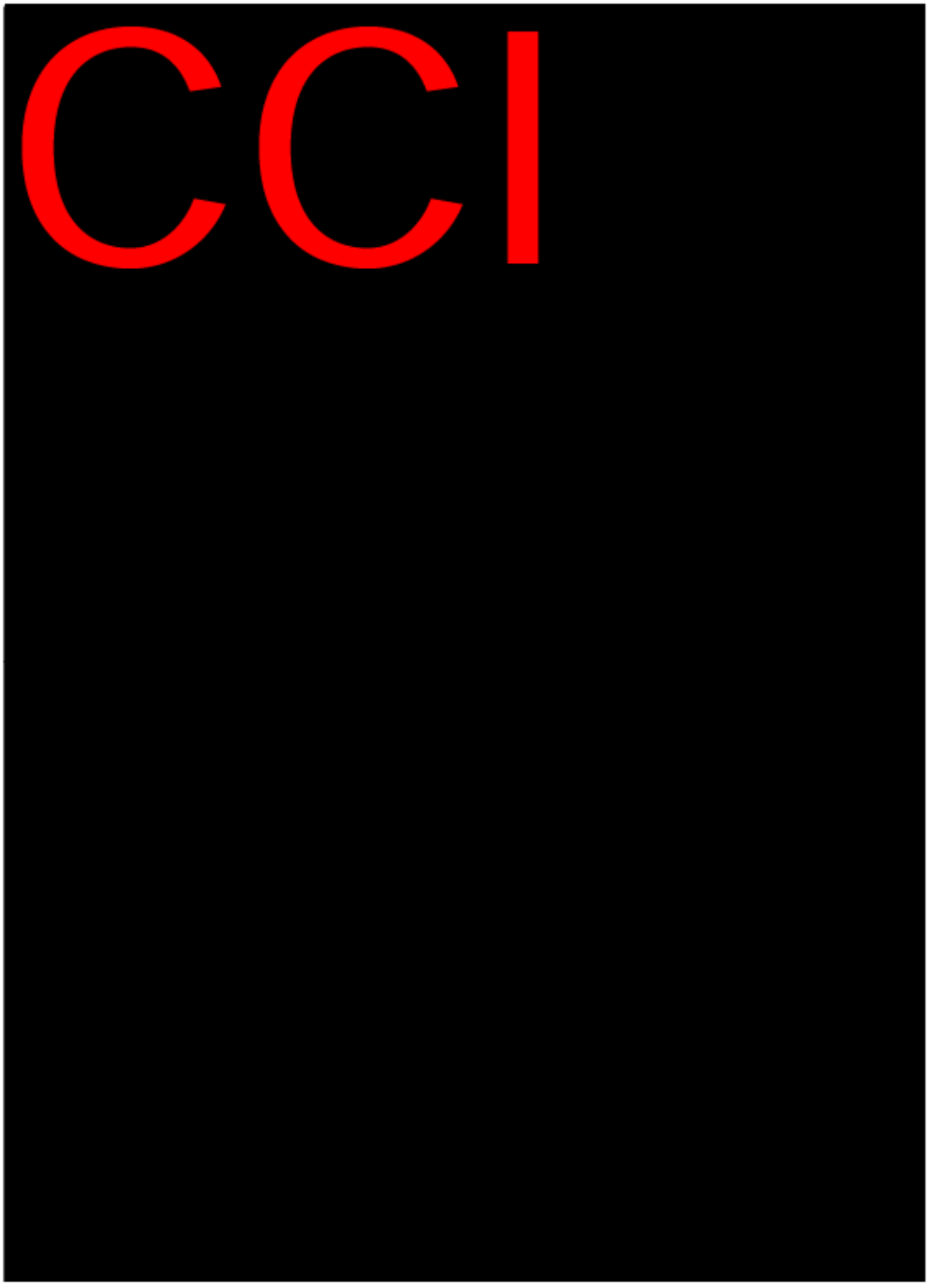
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Attachment 16. Sorafenib Adverse Events

The following drug-related adverse reactions and laboratory abnormalities (very common, ≥10%; common, 1 to <10%; uncommon, 0.1% to <1%) were reported from clinical trials of sorafenib (NEXAVAR; Bayer HealthCare Pharmaceuticals Inc., Wayne, New Jersey, USA):

- Cardiovascular
    - Common: congestive heart failure,*† myocardial ischemia and/or infarction
    - Uncommon: hypertensive crisis*
    - Rare: QT prolongation*
- Dermatologic
    - Very common: erythema
    - Common: exfoliative dermatitis, acne, flushing
    - Uncommon: folliculitis, eczema, erythema multiforme, keratoacanthomas/squamous cell cancer of the skin
- Digestive
    - Very common: increased lipase, increased amylase
    - Common: mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia
    - Uncommon: pancreatitis, gastrointestinal reflux, gastritis, gastrointestinal perforations,* cholecystitis, cholangitis
        - Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values
- General disorders
    - Very common: hemorrhage (including gastrointestinal* and respiratory tract* and uncommon cases of cerebral hemorrhage*), asthenia, pain (including mouth, bone, and tumor pain)
    - Common: decreased appetite, influenzalike illness, pyrexia
    - Uncommon: infection
- Hematologic
    - Very common: leukopenia, lymphopenia
    - Common: anemia, neutropenia, thrombocytopenia
    - Uncommon: INR abnormal
- Hypersensitivity
    - Uncommon: hypersensitivity reactions (including skin reactions and urticaria)
- Metabolic and nutritional
    - Very common: hypophosphatemia
    - Common: transient increases in transaminases
    - Uncommon: dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism, hyperthyroidism

- Musculoskeletal
    - Common: arthralgia, myalgia
- Nervous system and psychiatric
    - Common: depression
    - Uncommon: tinnitus, reversible posterior leukoencephalopathy*
- Renal and genitourinary
    - Common: renal failure
- Reproductive
    - Common: erectile dysfunction
    - Uncommon: gynecomastia
- Respiratory
    - Common: hoarseness
    - Uncommon: rhinorrhea, interstitial lung disease-like events (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis, and lung inflammation)
- In addition, the following medically significant adverse reactions were uncommon during clinical trials of sorafenib:
    - transient ischemic attack,
    - arrhythmia, and
    - thromboembolism.

  For these adverse reactions, the causal relationship to sorafenib has not been established.

* Adverse reactions may have a life-threatening or fatal outcome.
† Reported in 1.9% of patients treated with sorafenib (N=2276).

The following adverse drug reactions have been identified during postapproval use of sorafenib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Dermatologic: Stevens-Johnson syndrome and toxic epidermal necrolysis
- Hypersensitivity: angioedema, anaphylactic reaction
- Hepatobiliary disorders: drug-induced hepatitis, including reports of hepatic failure and death

Source: FDA, 2011.

Attachment 17. Protocol JBAK Amendment (e) Summary Phase 2 Study of LY2157299 in Patients with Hepatocellular Carcinoma

Overview

Protocol H9H-MC-JBAK Phase 2 Study of LY2157299 in Patients with Hepatocellular Carcinoma has been amended. The new protocol is indicated by Amendment (e) and will be used to conduct the study in place of any preceding version of the protocol.

Amendment (e) revisions are summarized as follows:

- Part E will be added to the study to explore LY2157299 given at 150 mg twice daily for 21 days, followed by 7 days off drug (cycle length= 28 days). This dose will be examined in approximately 23 patients.
- Amendment (e) includes the provision that Part D of Study JBAK will be conducted outside of the EU and clarification on how Part D expansion will be conducted. The Part D PK sampling schedule (Attachment 4) has been revised to include required sampling timepoints for ramucirumab PK concentrations.
- A reference to the appearance of the LY2157299 tablets has been removed.
- Editorial revisions have been made throughout the protocol.

Revised Protocol Sections

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

Protocol H9H-MC-JBAK(~~d~~e) Phase 2 Study of LY2157299 in Patients with Hepatocellular Carcinoma

This is an open-label, multicenter, multicountry, Phase 2 study of LY2157299 in patients with hepatocellular carcinoma. The study design consists of ~~3~~ 5 parts. In Part A, patients with alpha-fetoprotein (AFP) ≥1.5x ULN will be randomized to 2 cohorts based on initial dose of LY2157299 to be received (160 or 300 mg/day). In Part B, patients with AFP <1.5x ULN will receive LY2157299 300 mg/day. In Part C, patients with no prior systemic treatment will receive LY2157299 in combination with sorafenib. In Part D, patients will receive LY2157299 in combination with ramucirumab. In Part E, patients who have received at least one prior line of systemic therapy or who have not received prior treatment and are ineligible for sorafenib treatment will receive LY2157299 150 mg BID according to a 21 days on/7 days off schedule.

2. Synopsis

Name of Investigational Product: LY2157299	
Title of Study: Phase 2 Study of LY2157299 in Patients with Hepatocellular Carcinoma	
Number of Planned Patients/Subjects: Enrolled/Randomized: approximately ~~205~~235	**Phase of Development:** Phase 2
Length of Study: ~~5~~7.5 years Planned first patient visit: Q1 2011 Planned last patient visit: ~~October~~ July 2018	
Objectives: The primary objective of this study is to characterize both the time-to-progression (TTP) distributions and the effect on transforming growth factor beta (TGF-β)-associated serum biomarkers (for example, TGF-β, alpha-fetoprotein [AFP], E-cadherin) of study treatment in patients with hepatocellular carcinoma (HCC). The secondary objectives of the study are: • To evaluate the safety of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab in HCC patients • To evaluate the population pharmacokinetics (PK) of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab • To recommend which doses of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab to use in future trials recruiting HCC patients • To evaluate the safety and tolerability, pharmacokinetics and efficacy of LY2157299 as monotherapy administered according to a 21 days on/7 days off schedule • To characterize other time-to-event distributions, such as progression-free survival (PFS, based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 and modified RECIST [mRECIST], for HCC) and overall survival (OS) • To estimate antitumor efficacy using response rate (RR, based on RECIST 1.1 and mRECIST, for HCC) • To assess patient-reported outcome (PRO) measures of disease-specific symptoms and health-related quality of life (Functional Assessment of Cancer Therapy Hepatobiliary [FACT-Hep]) • To explore E-cadherin, pSMAD, and β-integrin (and other markers associated with epithelial-to-mesenchymal transition ~~(~~[EMT~~)~~] transformation and the TGF-β-associated signaling pathway) presence in the original diagnostic tumor tissue and optional posttreatment tumor tissue and the correlation of this with both clinical efficacy endpoints and biomarker response • To explore the utility of exploratory imaging techniques (for example, positron emission tomography [PET] scan, contrast echography) to assess treatment effect with LY2157299 as monotherapy and in combination with sorafenib when possible • To explore fibrosis-related biomarkers, such as Fibrotest	
Study Design: This is an open-label, multicenter, multicountry, Phase 2 study of LY2157299 in patients with hepatocellular carcinoma. The study design consists of ~~4~~5 parts. In Part A, patients with AFP ≥1.5x upper limit of normal (ULN) will be randomly assigned to 2 cohorts based on initial dose of LY2157299 to be received (160 or 300 mg/day). In Part B, patients with AFP <1.5x ULN will receive LY2157299 300 mg/day. In Part C, patients with no prior systemic treatment will receive LY2157299 (160 or 300 mg/day) in combination with sorafenib 400 mg twice daily (BID). In Part D, patients with Child-Pugh A liver disease will receive treatment with LY2157299 (160 or 300 mg/day) in combination with ramucirumab (8 mg/kg IV on Days 1 and 15 of each cycle). In Part E, patients with Child-Pugh Class A liver disease and any AFP who have received at least one prior line of systemic therapy or who have not received prior treatment and are ineligible for sorafenib treatment will receive LY2157299 150 mg BID according to a 21 days on/7 days off schedule.	

Diagnosis and Main Criteria for Inclusion and Exclusions:
Inclusion Criteria:
[1] Have histological evidence of a diagnosis of HCC not amenable to curative surgery.
[2] Have Child-Pugh Class:
Parts A and B: A or B7
Parts C and D: A
Part E: A
[3] Have serum AFP:
- Part A: ≥1.5x ULN
- Part B: <1.5x ULN
Criterion [3] applies for Parts A and B only.
[4] Have the presence of measurable disease as defined by the RECIST 1.1. A lesion that has been previously treated by local therapy will qualify as a measurable or evaluable lesion if there was demonstrable progression following locoregional therapy.
[5] Age ≥18 years
[6] Have given written informed consent prior to any study-specific procedures
[7] Have adequate organ function including:
- Hematologic: absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥50 x 10^9/L, and hemoglobin ≥8 g/dL.
- Hepatic: bilirubin ≤2.5 times ULN; alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) ≤5 times ULN. Prothrombin time international normalized ratio, ≤2.3; or prothrombin time limit is 6 seconds above control.
- Renal: Serum creatinine ≤1.5 times ULN or calculated creatinine clearance >45 mL/min.
Note: Small differences from the outlined laboratory values will be deemed as consistent with the protocol requirements provided that the following criteria are met: they are isolated, are transient, and are not reflective of a medical condition in the opinion of the investigator. Such differences are often a result of biological or laboratory equipment variability. To confirm that these results are within biological or laboratory equipment variability, repeat laboratory/hematological tests should be done prior to dosing the patient on Cycle 1 Day 1.

[8] Have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale.
[9] Have ~~either~~:
In Parts A and B:
- received sorafenib and have progressed or were intolerant to sorafenib, or
- are ineligible for sorafenib treatment (at the investigator's discretion).
In Part C: not received previous systemic treatment.
In Part D:
- received sorafenib and have progressed or were intolerant to sorafenib, or
- are ineligible for sorafenib treatment (at the investigator's discretion), or
- have not received prior systemic treatment (at the investigator's discretion).
In Part E:
- received at least one prior line of systemic therapy, or
- not received prior treatment and are ineligible for sorafenib treatment (at the investigator's discretion).

[10] In Parts A, B, ~~and~~ D and E: have discontinued sorafenib for at least 2 weeks.

Exclusion Criteria:
[15] Are currently enrolled in, or discontinued within the last 28 days from a clinical trial involving an investigational drug or device or not approved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
[16] Known HCC with fibro-lamellar or mixed histology.
[17] Presence of clinically relevant ascites.

[18] Liver transplant requiring increased immunosuppressive therapy. (Patients on maintenance immunosuppressive therapy after liver transplant are eligible for Parts A and B. Rapamycin analogues are not allowed.)
[19] Have received >1 line of systemic treatment in Parts A, B, and D.
[20] Have moderate or severe cardiac disease.

[21] Have serious preexisting medical conditions that, in the opinion of the investigator, cannot be adequately controlled with appropriate therapy or would preclude participation in this study.
[22] Females who are pregnant or lactating.
[23] Have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix) unless in complete remission and off all therapy for that disease for a minimum of 3 years.
At the discretion of the investigator, hormone-refractory prostate cancer patients who are stable on gonadotropin-releasing hormone (GnRH) agonist therapy and breast cancer patients who are stable on antiestrogen therapy (for example, an aromatase inhibitor) may have that treatment continued while they are enrolled in this study.
[24] Have active infection that would interfere with the study objectives or influence study compliance.
[25] For Part C, have a known hypersensitivity to sorafenib or its excipients.
[26] For Part D, have a serious illness or medical condition(s), including but not limited to the following:

a) The patient has undergone major surgery within 28 days prior to randomization or has undergone central venous access device placement within 7 days prior to randomization.
b) The patient has uncontrolled arterial hypertension ≥150 / ≥90 mm Hg despite standard medical management.
c) The patient is receiving ongoing therapy with nonsteroidal anti-inflammatory agents (NSAIDs) (eg, indomethacin, ibuprofen, naproxen, nimesulide, celecoxib, etoricoxib, or similar agents) or other antiplatelet agents (eg, clopidogrel, ticlopidine, prasugrel, dipyridamole, picotamide, indobufen, anagrelide, triflusal, or similar agents). Aspirin at dosages up to 100 mg/day is permitted.
d) The patient is receiving therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents. Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that the coagulation parameters defined in the inclusion criteria are met.
e) Uncontrolled thrombosis (including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within 6 months prior to randomization) or bleeding.
f) The patient has experienced any Grade 3 or 4 gastrointestinal bleeding or any variceal bleeding episode in the 3 months prior to randomization requiring transfusion, endoscopic or operative intervention (patients with any bleeding episode considered life-threatening during the 3 months prior to randomization are excluded, regardless of transfusion or intervention status). Patients who have esophageal or gastric varices that require immediate intervention or represent a high bleeding risk in the opinion of the investigator or consulting gastroenterologist or hepatologist are excluded.
g) Elective or planned major surgery to be performed during the course of the clinical trial.
h) Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to randomization.
i) Known allergy or hypersensitivity to monoclonal antibody treatment or any components used in the ramucirumab drug product preparation.
j) The patient's urinary protein is >1+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates ≥2+ proteinuria, then a 24-hour urine must be collected and must demonstrate <1000 mg of protein in 24 hours to allow participation in the study.
k) The patient has either a history of or current hepatic encephalopathy or current clinically meaningful ascites. *Clinically meaningful ascites* is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

Test Product, Dosage, and Mode of Administration:
Parts A and B: LY2157299 is administered orally by daily dosing morning and evening (BID) at either 80 or 150 mg per dose (total dosage of 160 or 300 mg daily) for 14 days, followed by 14 days with no study drug. (The exception is for patients who will have a Day 15 PK sample taken, who will omit the evening dose on Day 14.) This on/off schedule constitutes a cycle of 28 days. In extenuating circumstances, the "on study drug" window is allowable from Day 10 to Day 14.
Part C: LY2157299 is administered orally by daily dosing morning and evening (BID) at either 80 or 150 mg per dose (total dosage of 160 or 300 mg daily) for 14 days, followed by 14 days with no study drug. Sorafenib is administered orally by daily dosing morning and evening (BID) at 400 mg per dose (total dosage of 800 mg daily) for 28 days. This constitutes a cycle of 28 days.
Part D: LY2157299 is administered orally by daily dosing morning and evening (BID) at either 80 or 150 mg per dose (total dosage of 160 or 300 mg daily) for 14 days, followed by 14 days with no study drug. Ramucirumab is administered intravenously at 8 mg/kg on Days 1 and 15 of every cycle. This constitutes a cycle of 28 days.
Part E: LY2157299 is administered orally by daily dosing morning and evening (BID) at 150 mg per dose (total dosage of 300 mg daily) for 21 days, followed by 7 days with no study drug.

Planned Duration of Treatment Per Patient: Per patient, the screening period is no more than 4 weeks or 28 days before the first dose of LY2157299; the planned treatment duration is 6 cycles or approximately 24 weeks. However, patients may receive LY2157299 until their disease has progressed, the patient has died, or the patient discontinues for adverse events, investigator's judgment, or other reasons. Wash-out period: none.

Planned Follow-Up Observation Period Per Patient: Follow-up visits consist of a visit approximately 30 days after the last study treatment and any subsequent follow-up approximately every 60 days (approximately 2 months) (±7 days). Patients who have discontinued study treatment without progression will continue to be followed for progression. Every attempt should be made to gather all information every 2 months (radiological scans and survival), even if a patient starts a new anticancer therapy. All patients will be followed until death. Patients who have entered the treatment extension period will be followed for just 30 days after treatment discontinuation.

Reference Therapy, Dose and Mode of Administration: Not applicable

Criteria for Evaluation:
Efficacy: RECIST 1.1 and mRECIST, (mRECIST for HCC) for RR, TTP and PFS
Safety: International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0
Health Outcomes: PRO measures of disease-specific symptoms and health-related quality of life (FACT-Hep)
Bioanalytical: Plasma LY2157299/sorafenib/ramucirumab concentrations will be analyzed by liquid chromatography/mass spectrometry/mass spectrometry

Statistical Methods:

Outline of Design: Approximately ~~205~~235 Child-Pugh Class A or B7 patients with HCC will be enrolled into this study. In Parts A and B, patients were initially randomly assigned onto 1 of 2 doses, balanced based on AFP levels (≤400 ng/mL and >400 ng/mL), etiology, and whether sorafenib-naïve or not. A planned interim analysis after approximately 10 (for PK and acute safety) patients enrolled into each dose and completed 1 cycle was carried out. The second interim analysis for futility of 1 or both doses was not carried out but, as part of the continuous monitoring of safety, PK, and laboratory markers in patients with HCC, the sponsor noted that patients in both cohorts were staying on study beyond 4 months. An additional data review was carried out based on 64 enrolled patients, and ~~the~~a decision was made to ~~drop~~stop enrollment to the 160 mg/day dose and ~~to~~ continue ~~enrolling into~~ enrollment to the 300 mg/day dose until 70 patients ~~have been~~were treated ~~was made~~. The protocol was amended (Amendment [b]) to have 3 parts. The 2 cohorts planned in the original protocol and in Amendment (a) ~~will be~~were designated as Part A. Part B ~~will enroll~~enrolled approximately 40 patients with AFP levels <1.5x ULN and ~~treat~~treated them with 300 mg/day intermittent dosing. Two interim analyses ~~are~~were planned for ~~Amendment (b)~~ Part B – one after the last of ~~the~~ 70 patients with elevated AFP levels in Cohort 2 ~~have~~ started Cycle 1, and the second after 18 patients ~~have~~ enrolled into Part B and were actively followed for at least 3 months or ~~have~~ discontinued from study treatment. Part C ~~will enroll~~enrolled approximately ~~40~~47 Child-Pugh Class A patients and ~~will consist~~consisted of a safety lead-in ~~with~~of 2 dose-escalation cohorts followed by an expansion cohort where the selected dose(s) of the combination treatment ~~will be~~were evaluated. Part D will enroll approximately ~~15~~18 Child-Pugh Class A patients ~~and will consist of~~into 2 dose-escalation cohorts. Part E will initially enroll up to approximately 23 patients. This would give a total of approximately ~~205~~235 patients enrolled.

Safety: Summary statistics, plots, and listings for all safety data collected will be provided in aggregate and by dose in Part A and Part C, and in aggregate for Part B separately. Comparisons between doses and parts will be summarized for Part A and Part B, and may be compared to Part C. Data from Part D and Part E will be summarized separately from the data in Parts A, B, and C.

Clinical Efficacy: Time-to-event distributions will be characterized for each dose in each part (where data allow) using Kaplan-Meier methods, and various time-to-event parameters, such as median TTP, PFS, and OS and their rates at specified time points, will be estimated from their respective distributions. The hazard ratios between doses for patients with elevated AFP levels and between groups of patients with elevated AFP and AFP levels <1.5x ULN at 300 mg/day will be estimated. Sensitivity analyses using alternative models ~~will~~may also be performed. RR will be summarized by dose and part. Stratification factors used in the randomization ~~will~~of Part A may be included as covariates in analyses between doses. Beginning with Amendment (b), patients will no longer be randomized onto treatment, but the same covariates ~~will~~may be considered in analyses of clinical endpoints. Data from Part D and Part E will be summarized separately from the data in Parts A, B, and C.

~~Health Outcomes: Summary descriptive statistics by study part will be provided for the PRO data (FACT-Hep) at each time point and change from baseline. Time to worsening of symptoms will also be evaluated.~~

~~Pharmacokinetics: A population PK analysis will be performed on all patients receiving LY2157299. A PK analysis will be performed for sorafenib as well for some patients being enrolled in Part C. This analysis will explore the impact of covariates such as demographic factors and markers on the relevant PK parameters. The LY2157299 PK, when administered in combination with ramucirumab, will be characterized.~~

~~Pharmacodynamics: Changes in response biomarkers, such as pSMAD in tumor tissue (or other TGF-β related biomarkers) and lactate dehydrogenase, AFP, E-cadherin in serum will be estimated and may be correlated with clinical efficacy. Exploratory population PK/pharmacodynamic analyses may be conducted to identify the exposure-biomarker response relationship.~~

Health Outcomes: Summary descriptive statistics by study part will be provided for the PRO data (FACT-Hep) at each time point and change from baseline. Time to worsening of symptoms will also be evaluated.
Pharmacokinetics: A population PK analysis will be performed on all patients receiving LY2157299. A PK analysis will be performed for sorafenib as well for some patients enrolled in Part C. This analysis will explore the impact of covariates such as demographic factors and markers on the relevant PK parameters. In Part D, the LY2157299 and ramucirumab PK administered in combination will be characterized. In Part E, the PK of LY2157299, when administered according to a 21 days on /7 days off treatment schedule, will be characterized.
Pharmacodynamics: Changes in response biomarkers, such as pSMAD in tumor tissue (or other TGF-β-related biomarkers) and lactate dehydrogenase, AFP, E-cadherin in serum will be estimated and may be correlated with clinical efficacy. Exploratory population PK/pharmacodynamic analyses may be conducted to identify the exposure-biomarker response relationship.

4. Abbreviations and Definitions

IWRS	interactive web response system

5. Introduction

Different agents have been tested as second-line therapy in HCC patients (Table JBAK.~~5~~1). Time to progression without any treatment is estimated to be 2.7 months (Llovet et al. 2012).

Table JBAK.~~5.1~~.1. Examples of Experimental Treatments as Second-Line Therapy in Patients with Hepatocellular Carcinoma

Study	Patient (n)	Treatment	Time to Progression or Time to Treatment Failure (median months)	Method	Response Rate	OS (median, months)	Reference
Phase II	46	Brivanib	2.7	mWHO (assessed by PI)	4.3%	9.7	Finn et al. 2012
			1.77 (95% CI, 1.38–4.01)	mWHO (assessed by IRRC)	4.3%		
			6.9 (95% CI, 3.9–NR)	mRECIST (assessed by independent radiologist)	10.9%		
Phase III	263	Brivanib	4.2	mRECIST	11.5%	9.4	Llovet et al. 2012
	132	Placebo	2.7	mRECIST	1.9%	8.2	
Phase I/II	28	Everolimus	3.9 (95% CI, 2.1-5.5)	RECIST	4%	8.4	Zhu et al. 2011
Phase II	38	Sunitinib	2.9 ~~months~~ (95% CI, 0.5-15)	-	6%		Yau et al. 2011
Phase II	11	Sunitinib	3.2 ~~months~~	RECIST		8.4	Wörns et al. 2010
Phase II	18	Gemcitabine Oxaliplatin	PFS 3.2 (95 % CI, 2.3–3.9)			4.7	Mir et al. 2012
Phase III	283	Ramucirumab	3.48	RECIST	7.1%	9.17	Zhu et al. 2015
Phase III	573	Regorafenib	3.2	mRECIST	10.6%	10.6	Bruix et al. 2016

Abbreviations: CI = confidence interval; IRRC= independent response review committee; mRECIST = modified Response Evaluation Criterial in Solid Tumors; mWHO = modified World Health Organization; NR = not reached; OS = overall survival; PFS = progression free survival; PI – principal investigator.

5.1.4.1. Overall Conclusions

Collectively, the findings in the continuous 3- and 6-month daily-dosing toxicity studies, particularly the degeneration of the large blood vessels, imply that long-term, daily dosing of LY2157299 may carry a risk in patients for developing aneurysms. Reversibility was not assessed in the 3- or 6-month toxicity studies, but in a non-GLP reversibility study in rat, data indicate the cardiovascular lesions are partially reversible, but those that are still present following the recovery period are still adverse. The intermittent-dosing regimen in patients is based on the safety demonstrated in the rat and dog following 1 month of continuous daily dosing in which the NOEL for any effects in the heart was 150 and 20 mg/kg in the rat and dog, respectively, and a 3-month intermittent-dosing study in the rat in which the NOEL for any effects in the heart was 50 mg/kg (see Table JBAK.~~5.~~2 for margin-of-safety [MOS] calculations). Although the likelihood of occurrence or the extent and timing of such a risk observed after daily dosing is not known in humans, LY2157299 will be administered as an intermittent-dosing regimen in this patient population which has a poor prognosis and rapidly advancing cancer.

Table JBAK.~~5.2.~~2. Margin of Safety Based on NOEL to Cardiovascular Effects

5.1.5.1. Safety

As of 15 September 2015, approximately 696 patients and 20 healthy subjects have received treatment with LY2157299, either in monotherapy or in combination with chemotherapy. These include clinical trial patients with advanced/metastatic cancer, solid tumors, glioblastoma, pancreatic cancer, HCC and myelodysplastic syndromes (MDS).

Overall, few SAEs deemed by investigators to be associated with drug treatment have been reported. Most treatment-related SAEs have been reported in 1 patient except anemia (2 patients with HCC), cardiac failure (2 patients with MDS), neutropenia (1 patient with glioblastoma and 1 patient with HCC), thrombocytopenia (2 patients with glioblastoma), peritoneal hemorrhage (2 patients with HCC), and diarrhea (1 patient with glioblastoma and 1 patient with HCC). The SAE profile seems to differ when LY2157299 is used in patients with glioblastoma, MDS, and HCC, indicating a possibility that reporting rates are influenced by the underlying disease and there have been no trends or signals noted in the reported SAEs.

The most common TEAEs (≥10%) for LY2157299 monotherapy are fatigue (19%), anemia (18%), abdominal pain (18%), edema peripheral (15%), nausea (15%), asthenia (14%), diarrhea (14%), vomiting (14%), abdominal pain (12%), headache (12%), constipation (10%), decreased appetite (10%), and pruritus (10%). Most of these AEs were of mild or moderate severity.

The addition of LY2157299 to standard cancer treatments appeared to have no effect on the established toxicity profile of these standard therapies.

Extensive cardiac safety monitoring has been conducted in all clinical studies, and available data has shown no indication of a LY2157299-related cardiac toxicity.

The intermittent dosing regimen of 14 days on treatment with LY2157299 followed by 14 days off treatment (1 cycle = 28 days) that has been used in clinical development to date appears to be

well tolerated with no clinically significant valvulopathies or aneurysms reported or observed at dosages of up to 300 mg/day.

For additional details, please refer to the LY2157299 IB, Section 6.

5.1.5.2. JBAK: Brief Summary of Results to Date

At the time of Amendment (e), Part A and Part B of the study have completed. A total of 149 patients were enrolled (109 in Part A and 40 in Part B). Eighty-five percent of patients were male and the median age was 65 years. Fifty-six percent of patients had an ECOG performance status (PS) of 0 and 44% had a PS of 1. Eighty-six percent of patients had a Child-Pugh Class A score and 14% had a Class B score. Etiology of disease was a follows: hepatitis C 24%, hepatitis B 20%, alcohol 20%; multiple 9.4%. Overall, 83% of patients had received prior sorafenib. Eleven patients discontinued treatment due to AEs: 8 were considered related to study treatment. Grade 3/4 AEs possibly related to treatment were observed in 26 (17%) patients. Of these AEs, neutrophil count decrease was observed in 4 patients. Anemia, hypoalbuminemia, decreased bilirubin, fatigue and embolism were observed in 2 patients each. All other AEs occurred in just 1 patient. Median TTP was 11.9 weeks (95% CI: 6.3, 12.6) in Part A and 18.0 weeks (95% CI: 10.0, 24.0) in Part B. Median OS was 31.4 weeks (95% CI: 22.9, 40.6) in Part A and 73.0 weeks (95% CI: 45.4, 104.7) in Part B. The median OS for the overall population was estimated as 40.4 weeks (95% CI: 31.1, 52.4) (Giannelli et al. 2016).

Enrollment into Part C has completed and maturation of the data is awaited. Enrollment is ongoing in Part D of the study.

5.1.7. Rationale for Amendment (b)

Preliminary PK data from the first interim analysis (n=20 patients) suggest that patients administered 300 mg/day have higher exposures than previously observed for the same dose level (Study JBAH) during the treatment period. LY2157299 appears to be fully eliminated after the 14-days off period of a cycle (additional PK sampling is added to study the clearance of LY2157299). The lowest exposure level (ie, most conservative) in the most sensitive nonclinical species administered LY2157299 in a clinically relevant dosing schedule (2 weeks on/2 weeks off) in which cardiac effects were observed was 24 µg*hr/mL (Table JBAK.~~5.~~2). The findings at this dose level (150 mg/kg) consisted of a single male rat (n=10/group) with minimal inflammation in the aortic valve and ascending aorta. Administration of 300 mg/day to patients with HCC may result in higher than anticipated exposures; however, due to the clinical safety profile observed thus far and the benefit:risk in this patient population, this approach is considered acceptable.

5.1.10. Rationale for Amendment (e)

The protocol is being amended to add a Part E that will allow the evaluation of the safety and tolerability, pharmacokinetics and efficacy of LY2157299 administered according to a 21 days on/7 days off schedule.

Across the clinical development program at the time of Amendment (e), LY2157299 has shown a favorable short- and long-term toxicity profile in different studies and activity in different tumor types.

In light of cardiotoxicity observed in nonclinical trials of LY2157299, comprehensive cardiac safety monitoring was implemented in all clinical trials of LY2157299, including Study JBAK, and has been ongoing until the time of this amendment.

Using a data cut-off date of 15 September 2015, Lilly has performed a cross-study cardiovascular (CV) safety analysis of 745 patients from 10 completed and ongoing unblinded studies of LY2157299, including patients assigned to standard of care control arms who did not receive LY2157299. This analysis included a review of CV-related TEAEs and SAEs (with a focus on patients with increased valvular insufficiency and vascular-related hemorrhage/aneurysm, as well as patients with events of heart failure) and a correlation of TEAE/SAE data with central echocardiography findings, chest CT scan and/or MRI findings, cardiac laboratory markers (BNP, cystatin C, and troponin I) and central ECG findings. The cumulative results of this cross-study analysis did not identify any concerning trends in AEs, in particular those related to valvulopathies or aneurysms.

As described in Section 5.1.4, nonclinical toxicology data have determined a no-effect level for CV lesions that is higher than the observed and anticipated exposures in Study JBAK and other clinical trials. There is also no evidence of accumulation in patients given multiple doses of LY2157299 at 150 mg BID, suggesting that daily exposures on a schedule with increased days of dosing will remain lower than the no-effect-level for CV lesions characterized in toxicology studies.

In view of these clinical and nonclinical observations, Lilly has proposed and received endorsement from the United States (US) Food and Drug Administration to explore a new treatment schedule for LY2157299 in Part E of amended Study JBAK. This schedule will dose LY215729 at 150 mg twice daily for 21 days, followed by 7 days off drug (cycle length= 28 days). The goal is to improve upon the efficacy that has been observed in patients receiving LY2157299 on a 14 days on/14 days off schedule by increasing time on target and thereby limiting chances for tumor regrowth and resistance.

Amendment (e) also includes the provision that Part D of Study JBAK will be conducted outside of the European Union (EU) and clarification on how Part D expansion will be conducted.

Attachment 17 lists changes made in ~~the~~ protocol amendment~~.~~ (e).

6.2. Secondary Objectives

- To recommend which doses of LY2157299 as monotherapy and in combination with sorafenib or ramucirumab to use in future trials recruiting HCC patients
- To evaluate the safety and tolerability, pharmacokinetics and efficacy of LY2157299 as monotherapy administered according to a 21 days on/7 days off schedule

- To characterize other time-to-event distributions, such as progression-free survival (PFS, based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 and modified RECIST [mRECIST], for HCC) and OS

7.1. Summary of Study Design

Study JBAK is a multicenter, randomized trial characterizing the TTP distribution of 2 dose levels of LY2157299 in patients with Child-Pugh Class A or B HCC ~~patients~~.

Approximately ~~205~~235 patients will be enrolled into the study: ~~107~~ 109 have been enrolled into Part A, 40 into Part B, ~~40~~47 into Part C, ~~and 15 in~~approximately 18 into Part D and approximately 23 into Part E.

Starting with Amendment (~~d~~e), there are ~~4~~5 parts to this study: ~~Child-Pugh A and B7 patients are enrolled in Part A and Part B;~~

Parts A and B ~~are~~

Part A and Part B enrolled patients with Child-Pugh Class A and B7 status HCC, distinguished ~~based on~~by baseline AFP levels~~. Parts A and B enrolled Child-Pugh A and B7 patients~~ , who had either progressed on sorafenib or were ineligible to receive sorafenib~~, whereas Part C~~. Enrollment is ~~enrolling Child-Pugh A patients who have not received previous systemic therapy.~~ complete with 109 patients enrolled into Part ~~D of the study will enroll Child-Pugh A patients~~A and 40 into Part B.

In Part A, patients with AFP ≥1.5x ULN ~~will be~~were randomized to 2 cohorts based on initial dose of LY2157299 to be received (160 or 300 mg/day). Eligible patients ~~will be~~were randomized ~~into~~to 1 of these cohorts (the 2 cohorts being balanced as far as possible for AFP levels, etiology, and whether or not sorafenib-~~-naïve or not at both planned interims~~) and ~~the final analysis) and will receive~~received LY2157299 for 14 days followed by 14 days of rest (Figure JBAK.~~7~~.1).

At this point, Amendment (b) was implemented to continue enrolling into Cohort 2 of Part A and to initiate enrollment into Part B and included changes to the planned interim analyses.

~~In Part B, patients with AFP <1.5x ULN will receive LY2157299 300 mg/day for 14 days followed by 14 days of rest (Figure JBAK.7.1). The third interim analysis will occur after 18 patients have been~~ The second planned interim analysis for Part A (based on N=106 patients, Cohorts 1 and 2) was completed after the last patient had enrolled into Cohort 2 (n=69) and started Cycle 1. Detailed information is given in Section 12.2.14 (Interim Analyses). Enrollment ~~continues~~continued during all data reviews and interim analyses.

In Part B, patients with AFP <1.5x ULN received LY2157299 300 mg/day for 14 days followed by 14 days of rest (Figure JBAK.1). The third interim analysis occurred after 18 patients had been treated and completed 3 cycles or discontinued from study treatment. Detailed information is given in Section 12.2.14 (Interim Analyses).

Figure JBAK~~.7.1~~.1. Illustration of study design for Protocol H9H-MC-JBAK Parts A and B.

Part C ~~will evaluate~~

Part C evaluated LY2157299 in combination with sorafenib in patients with advanced HCC and Child-Pugh Class A status who ~~have~~had not received previous systemic treatment. Up to 40 patients ~~may~~were planned to be enrolled. Enrollment is complete and a total of 47 patients have been treated.

Part C ~~comprises~~comprised a safety lead-in of 2 cohorts followed by an expansion phase with selected safe dose(s) (Figure JBAK.~~7.~~2). Patients enrolled in Cohort 1 ~~will be~~were administered LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle. Three patients ~~will~~ were planned to be enrolled ~~on~~in Cohort 1; if no dose-limiting toxicities (DLTs) (related to LY2157299 or combination regimen) ~~are~~were observed in Cycle 1, 3 patients ~~will~~were to be treated ~~on~~in Cohort 2 at LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle. If a DLT related to LY2157299 or combination regimen ~~is~~was observed in either cohort in the first 3 patients in Cycle 1, then that cohort ~~will~~was to be expanded to include an additional 3 patients. Six to 12 patients ~~may~~were planned to be enrolled in the safety lead-in, depending on the observed DLTs. See Section 9.1.5 for more detailed dose escalation and expansion criteria. PK sampling ~~will be~~was conducted in Cycle 1 with the intent to assess drug-drug interactions between LY2157299 and sorafenib (Attachment 4).

Depending on the results from the safety lead-in cohorts and analysis from Parts A and B, the expansion cohort ~~will~~was to consist of 1 of the following:

- Single treatment group: LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle, or
- Single treatment group: LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 on a 28-day cycle, or
- Two treatment groups: LY2157299 80 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28 versus LY2157299 150 mg BID on Days 1 to 14 in combination with sorafenib at 400 mg BID on Days 1 to 28. Both cohorts ~~will~~were to be on a 28-day cycle.

Patients enrolled in the safety lead-in cohorts ~~may~~were to continue treatment as per that cohort.

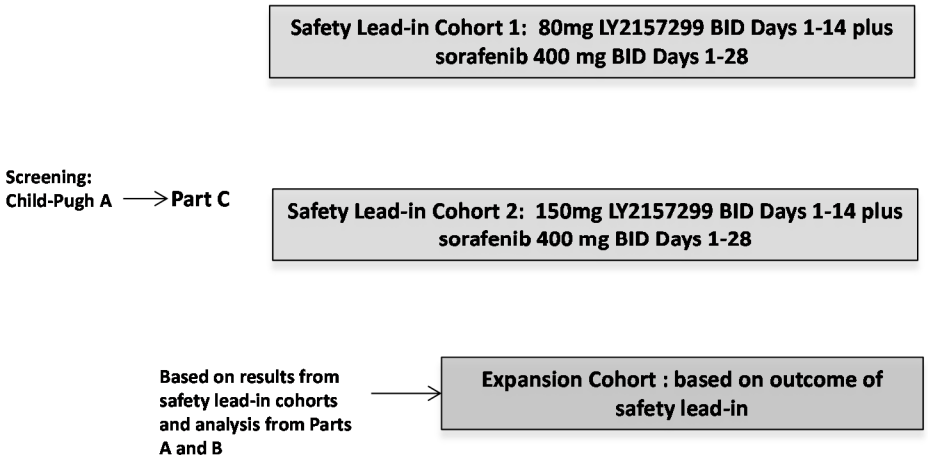


Figure JBAK~~.7.2~~.2. Illustration of study design for Protocol H9H-MC-JBAK Part C.

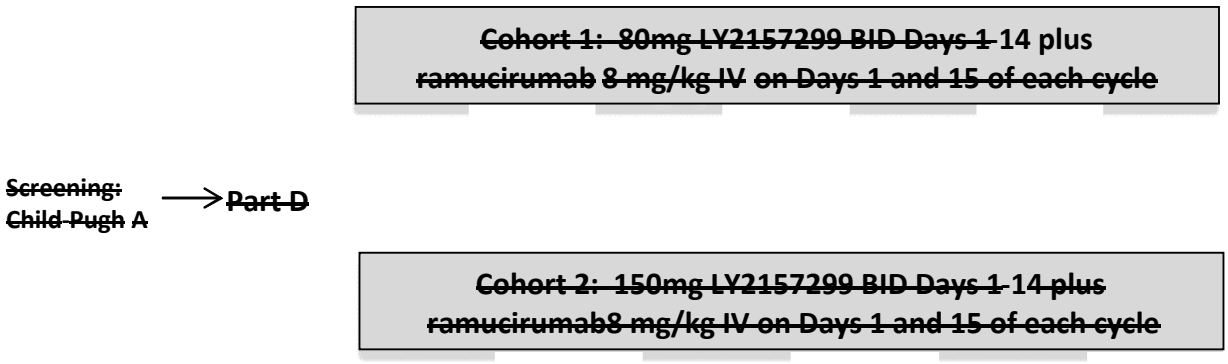
Part D

Part D will be conducted outside of the EU and will evaluate LY2157299 in combination with ramucirumab in patients with advanced HCC and Child-Pugh Class A status. ~~Up to approximately 15 patients may be enrolled.~~

Part D comprises 2 cohorts (Figure JBAK.~~7.~~3). Patients enrolled in Cohort 1 will be administered LY2157299 80 mg BID on Days 1 to 14 in combination with ramucirumab administered at 8 mg/kg as an intravenous (IV) infusion on Days 1 and 15 of every cycle. Approximately 18 patients may be enrolled to allow the selected dose to be expanded to approximately 15 patients in total.

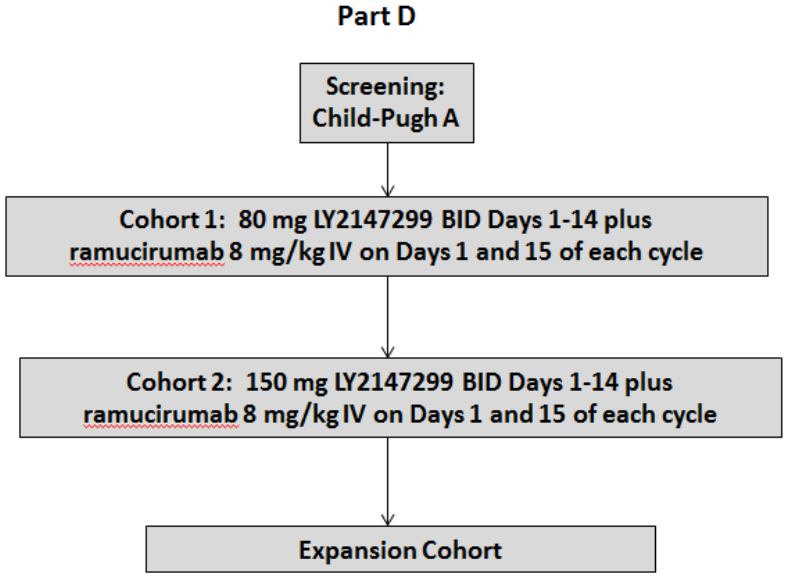
Three patients will be initially enrolled on Cohort 1; if no dose-limiting toxicities (DLTs) (related to LY2157299 or the combination regimen) are observed in Cycle 1, then 3 patients will be treated on Cohort 2 at LY2157299 150 mg BID on Days 1 to 14 in combination with ramucirumab 8 mg/kg administered as an IV infusion on Days 1 and 15 of every cycle. If a DLT related to LY2157299 or ~~combination regimen is observed in either cohort in the first 3 patients in Cycle 1, then that cohort will be expanded to include an additional 3 patients.~~ the combination regimen is observed in the first 3 patients in Cycle 1 of Cohort 1, Cohort 1 will enroll an additional 3 patients. If no further DLTs are observed, Cohort 2 will be opened. If 1 or more additional DLTs are observed in Cohort 1, Part D will close. If Cohort 2 is opened and no DLTs are observed in the first 3 patients, Cohort 2 will be expanded until approximately 15 patients have been enrolled. If 1 DLT is observed in Cycle 1 in the first 3 patients in Cohort 2, another 3 patients will be enrolled. If 2 or more DLTs are observed in the first 3 patients or 1 or more DLTS are observed in the additional 3 patients in Cohort 2, a safety review by Lilly and the investigators will occur to decide whether to expand Cohort 1. If no further DLTs are observed in Cohort 2, Cohort 2 will be expanded until a total of approximately 15 patients have been enrolled at this dose. See Section 9.1.5 for more detailed dose escalation and expansion criteria.

PK sampling will be conducted in Cycles 1 and 2 with the intent to assess changes in LY2157299 and ramucirumab exposure when ~~coadministered with ramucirumab~~ administered in combination (Attachment 4).



~~Abbreviations: BID = twice daily; IV = intravenous.~~

~~**Figure JBAK.14.1. Illustration of study design for Protocol H9H-MC-JBAK Part D.**~~



Abbreviations: BID = twice daily; IV = intravenous.

Figure JBAK.3. Illustration of study design for Protocol H9H-MC-JBAK Part D.

Part E

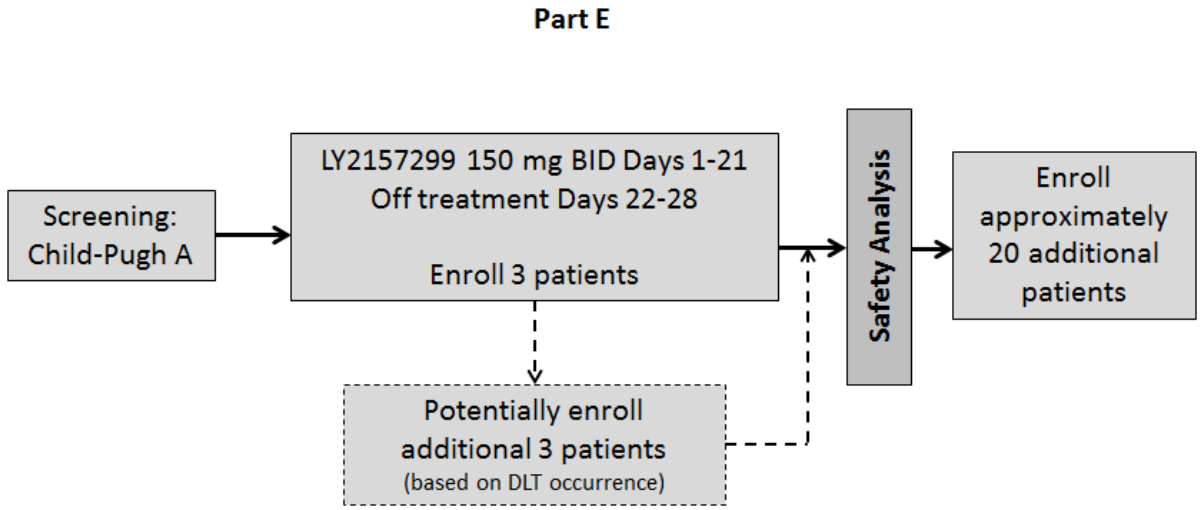
Part E will evaluate the safety, tolerability, pharmacokinetics and efficacy of LY2157299 given according to a 21 days on/7 days off schedule in patients with Child-Pugh Class A HCC who have received at least one prior line of systemic treatment or who have not received prior

treatment and are ineligible for sorafenib treatment (at the investigator's discretion). Up to approximately 23 patients may be enrolled.

Figure JBAK.4 shows the Part E study design.

It is planned that Part E will initially enroll up to 3 patients. Enrollment will halt after the first 3 patients have received their first dose of treatment. If a patient discontinues study treatment within the first cycle of therapy for any reason other than a dose-limiting toxicity (DLT), that patient may be deemed unevaluable and replaced. A safety evaluation will occur after the third evaluable patient has completed one cycle of therapy. Dose-limiting toxicities will be as defined in Section 9.1.5.1. If DLTs are observed in 2 of the first 3 patients dosed, Part E will close. If DLTs are observed in 1 of the 3 patients, a safety assessment will occur after the next 3 evaluable patients have completed 1 cycle. If the schedule is deemed to be tolerable (<33% DLTs in Cycle 1 as well as consideration of the overall safety profile from later cycles), additional patients will be enrolled so that data from approximately 20 patients will be available to better characterize the safety of the schedule and allow comparison to safety, pharmacokinetics and efficacy results in other cohorts.

Recognizing that potential CV effects may occur after the initial DLT period, patients will be regularly monitored according to a stringent schedule and as part of a trial level safety review. Trial level safety reviews will occur approximately every 3 months, beginning after the initial DLT evaluation period.



Abbreviation: BID = twice daily.

Figure JBAK.4. Illustration of study design for Protocol H9H-MC-JBAK Part E.

All Study Parts

One cycle is defined as 28 days (a minimum of 26 days and a maximum of 31 days~~: the~~). The treatment period for LY2157299 must be a minimum of 10 days and a maximum of 14 days~~;~~ (for

Parts A, B, C and D) and 21 days (for Part E); the "off-treatment" period can vary to ensure an overall cycle length of 26 to 31 days). In extenuating circumstances, the "on study drug" window for LY2157299 is allowable from Day 10 to Day 14. (In Part C and D safety lead-in Cycle 1 ~~and Part D Cycle 1,~~, patients must have received 14 days of LY2157299 treatment). For Part E Cycle 1, all patients must receive 21 days of treatment, followed by 7 days off treatment. If patients are not evaluable for ~~safety~~DLT assessment and/or PK in Cycle 1 of Part C or Part D safety lead-in, or Cycle 1 ~~of~~ Part ~~D~~E, the patients will be replaced.

Per patient, the screening period is no more than 4 weeks or 28 days before the first dose of LY2157299; the planned treatment duration is 6 cycles or approximately 24 weeks, but patients may continue to receive study drug if they are still benefiting from treatment in the opinion of the investigator and Lilly physician. Follow-up visits ~~consist of a visit~~will occur approximately 30 days after the last day of study treatment and ~~any subsequent follow-up~~subsequently approximately every 60 days (approximately 2 months~~) (±~~ [±7 days~~).~~]).

In case of the occurrence of severe toxicities in later cycles in patients ~~being~~ treated with either LY2157299 monotherapy or ~~with~~ LY2157299 in combination with ramucirumab or sorafenib, the sponsor will review and choose a lower dose or discontinue the patient, if necessary.

~~This Phase~~The final analysis for Parts A and B will be conducted after the study objectives for these 2 parts have been met. This is likely to be after approximately 30 deaths have occurred in Part B in order to have a reasonable estimate of overall survival in this patient group (AFP <1.5x ULN). ~~study~~

Part C will be considered complete and the final analysis initiated once 85% of events for survival analysis in the expanded cohort in Part C have occurred ~~and patients in~~ .

Part D ~~have~~will be considered complete and the final analysis initiated after the last patient has discontinued from study treatment ~~(including~~and completed at least the 30-day follow-up visit ~~(~~[Visit 801~~). Patients~~].

Part E will be considered complete and the final analysis initiated after the last patient has discontinued from study treatment and completed at least the 30-day follow-up visit [Visit 801].

At the time all parts of the study are considered complete, the study will be considered complete and those patients still on treatment ~~at the time that the study is considered complete~~ may enter the treatment extension period and continue to receive the study treatment (see Section 7.1.1).

All patients will be followed for OS until study completion.

End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study~~.~~ (this includes all patients who enter the extension period). The European Union (EU) has additional reporting requirements associated with the end of study. Consult regional standard operating procedures (SOPs) for further information.

7.1.1. Extension Period

After study completion (~~ie,~~i.e., study objectives met, see Section 7.1), all patients who are on study treatment (LY2157299 alone or LY2157299 with sorafenib ~~[~~in Part C~~] or,~~ LY2157299 with ramucirumab ~~[~~in Part D~~]~~), or LY2157299 alone in Part E) and who are eligible for the extension period may continue to receive study treatment until one of the criteria for treatment discontinuation is met (Section 8.3.1). Patients who are no longer on study treatment at the time of study completion and who have completed at least the 30-day follow-up visit (V801) will be discontinued from long-term follow-up and therefore reach the end of the study, unless they are being followed due to unresolved safety concerns. Lilly will notify investigato rs when the extension period begins.

~~All~~During the extension period, all AEs and study drug exposure will be reported on the case report form (CRF). SAEs will also be reported on the CRF and to Lilly Global Patient Safety (see Section 10.2.1.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

All patients in the extension period will be treated following the Study Schedule (see Attachment 1). This will ensure that appropriate risk/benefit ~~assessment~~assessments are conducted for all patients.

The patient's participation in the extension period will end after study drug(s) is discontinued. The date and reason for treatment discontinuation will be collected on the CRF. Data will be collected until 30 days after the patient has been discontinued from study treatment and at this point, the patient will have ended the study. If the patient dies within the 30-day follow-up period, the reason for study discontinuation will be "Death~~,~~"", and the cause and date of death recorded. Otherwise, the reason for study discontinuation will be noted as "Completed~~.~~"". There will be no long-term ~~postdiscontinuation~~post-discontinuation follow-up period for these patients, unless any safety concerns have not resolved. Requests for updates ~~of~~on survival may ~~be requested~~occur.

After the last of the patients in the extension period has completed their 30-day follow-up period, an addendum report will be written listing the details of data collected from patients entered ~~on~~in this phase. The addendum report will not be delayed due to any patients ~~being~~continuing in long-term follow-up, but will note those patients ~~who are~~ still in long-term follow-up due to unresolved safety issues.

7.2. Discussion of Design and Control

~~This~~Part A of this open-label, multicenter, ~~multicountry~~multi-country Phase 2 study ~~began with~~of patients randomized ~~onto~~to receive 1 of 2 doses of LY2157299 is an appropriate design for assessing antitumor activity and tolerability in ~~this~~an HCC patient population~~, and who have~~ with no alternative therapy~~. The~~ options, including patients who the investigator ~~may decide~~decides not to give sorafenib ~~(Parts A and B)~~ based on its toxicity profile, the condition of

the patient, the institutional practice guidelines (see guidelines in Attachment 15), ~~and~~or other reasons that justify not administering sorafenib.

~~TTP is recommended as the main time-to-event endpoint to capture possible antitumor benefits in Phase 2 trials testing molecular-targeted therapies in HCC because it is less vulnerable (only progression captured) than composite endpoints (Llovet et al. 2008; Thomas et al. 2010).~~

The requirement of including patients ~~in Part A~~ with ~~an~~ elevated AFP (≥1.5 x ULN) in Part A is based on previous studies suggesting that patients with elevated AFP may also have increased levels of TGF-β1 and thus have an activated TGF-β pathway. ~~For Part B, it was decided to evaluate the effects~~The enrollment of ~~LY2157299 in~~ patients with AFP <1.~~5x~~5 x ULN ~~to have an overall~~into Part B, will allow a comprehensive assessment of LY2157299 efficacy in all HCC patients. Patients will be enrolled into Part A or B based on the local AFP assessment ~~into Part A or Part B~~. For the final study assessment, the centrally collected AFP values will be used. At enrollment, the local AFP value may be higher or lower than the centrally-~~-~~assessed AFP values~~,~~ and this will not constitute a protocol violation. ~~Part C will allow safety and efficacy assessment of LY2157299 combination with sorafenib in first-line patients. Sorafenib is the approved agent in first-line HCC. Part D will allow safety assessment of LY2157299 in combination with ramucirumab.~~

Part C will allow safety and efficacy assessment of LY2157299 combination with sorafenib as first-line treatment for HCC. Sorafenib is the approved agent for first-line treatment of HCC.

Part D will allow a safety assessment of LY2157299 in combination with ramucirumab.

Part E will allow assessment of the safety and tolerability, pharmacokinetics and efficacy of LY2157299 administered according to a 21 days on/7 days off schedule, as well as comparison of these endpoints to that observed in patients on the 14 days on/14 days off schedule. At least approximately 20 patients must complete 21 days of therapy in order to have sufficient information to assess tolerability of the regimen.

8.1. Inclusion Criteria

[1] Have histological evidence of a diagnosis of HCC not amenable to curative surgery.

[2] ~~Have~~Are Child-Pugh Class:

- Parts A and B: A or B7 (see Attachment 5)

- Parts C and D: A

- Part E: A

[5] ~~Age~~Are age ≥18 years.

[6] Have given written informed consent prior to any study-specific procedures.

[9] Have ~~either~~:

In Parts A and B:

- received sorafenib and have progressed or were intolerant to sorafenib, or

- are ineligible for sorafenib treatment (at the investigator's discretion).

In Part E:

- received at least one prior line of systemic therapy, or

- not received prior treatment and are ineligible for sorafenib treatment (at the investigator's discretion).

[10] In Parts A, B, and D and E: have discontinued sorafenib for at least 2 weeks.

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [15] eliminates drugs that cannot be mapped to a standard drug dictionary or for which little data are known to analyze the potential relationship of AEs or drug interactions.

Exclusion Criterion [20] excludes patients with compromised cardiac function that could be at risk when receiving LY2157299. Based on the nonclinical toxicology assessment, patients with cardiac insufficiency or damage to large vessels of the heart will be carefully screened. All moderate and severe cases of cardiac insufficiency will be excluded. Because of the average age of most patients eligible for this study, mild or minimal cardiac disease is commonly present, and therefore these patients will not be excluded (Singh et al. 1999). If CT scan of the chest cannot be performed, MRI can ~~also~~ be used as an alternative imaging procedure.

9.1. Treatments Administered

Patients will keep a study diary to document that they are taking LY2157299 (Parts C, D and ~~D~~E) and sorafenib (Part C only) correctly.

9.1.1. Parts A and B

Table JBAK~~.9.1~~.3. Treatment Regimens for Parts A and B

LY2157299	Daily Dose	Schedule	Time of Day
Part A (Cohort 1)	80 mg BID LY	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
Part A (Cohort 2) and Part B	150 mg BID LY	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.

Abbreviations: BID = twice daily; LY = LY2157299; PK = pharmacokinetic.

Note: For patients who will have a Day 15 PK sample taken, the evening dose on Day 14 will be omitted to allow for a 24-hour time period between the Day 14 morning dose and the Day 15 PK sample.

In extenuating circumstances, the 'on study drug' window is allowable from Day 10 to Day 14.

9.1.2. Part C

Part C comprises a safety lead-in of 2 dose-escalation cohorts followed by an expansion phase with selected dose(s). This part involves characterization of LY2157299 administered at either

80 mg BID or 150 mg BID for 14 days followed by 14 days off and sorafenib 400 mg BID for 28 days administered orally to Child-Pugh Class A HCC patients. LY2157299 and sorafenib need to be taken at the same time, within a 15-minute window. A cycle is defined as 28 days. Table JBAK.~~9.2~~4 shows the proposed dose levels and schedule for Part C.

Table JBAK.~~9.2.~~4. Treatment Regimens for Part C

	Daily Dose	Schedule	Time of Day
Safety lead-in Cohort 1	80 mg BID LY plus	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
	400 mg BID sorafenib	Daily	Take in the morning and evening with LY dose
Safety lead-in Cohort 2	150 mg BID LY plus	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
	400 mg BID sorafenib	Daily	Take in the morning and evening with LY dose
Expansion cohort	Recommended LY dose(s) from safety lead-in plus	Daily 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
	400 mg BID sorafenib	Daily	Take in the morning and evening with LY dose

Note: For patients who will have a Day 15 PK sample taken, the evening dose on Day 14 will be omitted to allow for a 24-hour time period between the Day 14 morning dose and the Day 15 PK sample.
In extenuating circumstances, the "on study drug" window for LY2157299 is allowable from Day 10 to Day 14.
Abbreviations: BID = twice daily; LY = LY2157299; PK = pharmacokinetic.

9.1.3. Part D

A cycle is defined as 28 days. Table JBAK.~~9.3~~5 shows the proposed dose levels and schedule for Part D.

Table JBAK.~~9.3~~.5. Treatment Regimens for Part D

	Dose	Schedule	Time of Day
Cohort 1	80 mg BID LY plus	Daily by oral administration 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.
	8 mg/kg ramucirumab	Days 1 and 15 each cycle by IV administration (given over 60 min)	On Day 1 of each cycle, morning within 30 min of LY2157299 administration; on Day 15 of each cycle, morning
Cohort 2	150 mg BID LY plus	Daily by oral administration 14 days on/14 days off	Morning and evening for 14 days and then paused for 14 days.

8 mg/kg ramucirumab	Days 1 and 15 each cycle by IV administration (given over 60 min)	On Day 1 of each cycle, morning within 30 min of LY2157299 administration; on Day 15 of each cycle, morning

Note: For patients who will have a Day 15 PK sample taken, the evening dose on Day 14 will be omitted to allow for a 24-hour time period between the Day 14 morning dose and the Day 15 PK sample.
In extenuating circumstances, the on-study-drug window for LY2157299 is allowable from Day 10 to Day 14.
Abbreviations: BID = twice daily; IV = intravenous; LY = LY2157299; min = minutes; PK = pharmacokinetic.

9.1.4. Part E

In Part E, LY2157299 will be administered orally at 150 mg BID for 21 days followed by 7 days off. A cycle is defined as 28 days. Section 9.1.5.1 details the DLT criteria that will be used. Table JBAK.6 shows the proposed dose level and schedule for Part E.

Table JBAK.6. Treatment Regimen for Part E

Dose	Schedule	Time of Day
LY2157299 150 mg BID	Daily by oral administration 21 days on/7days off	Morning and evening for 21 days and then paused for 7 days

Abbreviations: BID = twice daily.

9.1.5. Criteria for Dose Escalation (Parts C and D)

By nature of being a dose-escalation safety assessment, data will be evaluated on an ongoing basis until the MTD is determined, as defined in Section 9.1.4~~4~~5.1. The maximum dose of LY2157299 will be 150 mg BID. Safety data, in particular AEs, will be the primary criteria for the dose escalation. The dose will be escalated following assessment of toxicity using the standard scoring system, CTCAE version 4.0, established by the National Cancer Institute (NCI). Any AEs related to LY2157299 or sorafenib (Part C) or ramucirumab (Part D) will be considered as toxicities.

~~In this part, intrapatient~~Intrapatient dose escalation is not permitted and dose escalation to the next cohort cannot occur without prior discussion and agreement between the investigator and the responsible Lilly clinical research physician (CRP). The decision will be documented in writing.

9.1.5.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition (Parts C, D and ~~D~~E)

A DLT is defined as an AE during Cycle 1 in Cohorts 1 or 2 that is related to the LY2157299 and sorafenib combination regimen ~~or~~in Part C, to the LY2157299 and ramucirumab combination regimen in Part D, or to LY2157299 administered on a 21 days on / 7 days off schedule in Part E and fulfills any 1 of the following ~~criterion~~criteria using ~~the~~ NCI CTCAE v 4.0:

For the purpose of this study, the MTD is defined as the highest tested dose in each part that has <33% probability of causing a DLT during Cycle 1.

As patients receive more cycles of treatment, investigators, together with the Lilly CRP, can declare a DLT-equivalent toxicity if a patient is experiencing increasing toxicity during treatment in later cycles (ie, other than Cycle 1), and it becomes clear that it will not be possible to complete the treatment without exposing the patient to excessive risk.

Once the MTD has been defined, ~~the expansion cohort(s) in Part C~~that dose level will be ~~opened~~expanded in Parts C, D and E.

If ~~either~~ toxicities are observed in the first cycle that would meet the DLT criteria defined above for Cohorts 1 and 2 or DLT-equivalent toxicities occur in 33% or more of patients within ~~this~~the cohort ~~expansion~~expansions in Part C, D and E, then investigators and the Lilly CRP will assess the nature and severity of these toxicities. The safety review and decision will be documented in writing.

9.2. Selection and Timing of Doses

For Part D and Part E, LY2157299 ~~(for Part D)~~ should be taken mornings and evening approximately 12 hours apart. Patients should take the agent preferably 1 hour before a meal.

In Part D, ramucirumab should be given in the mornings. On Day 1 of each cycle, LY2157299 should be taken within 30 minutes before the start of ramucirumab treatment.

Tablets should be swallowed whole and not split, crushed, or dissolved for administration.

9.3.1. LY2157299

~~The appearance of the tablet is white.~~LY2157299 will be provided as tablets in blister packs. All materials must be stored at room temperature within temperature range specified on the material label. The material will be labeled according to regulatory requirements of the country. Should the type of clinical trial material packaging change, it will adhere to country-specific regulations.

9.4. Method of Assignment to Treatment

In Part E, patients who have received at least one prior line of systemic therapy or who have not received prior treatment and are ineligible for sorafenib treatment (at the investigator's discretion) and who meet all criteria for enrollment will be assigned by the IWRS to receive LY2157299 150 mg BID dosage after completing the screening visit.

9.5.1. LY2157299

If dosing is delayed for more than 2 weeks, the patient should be withdrawn from the study. ~~Patients~~

For Parts A and B, patients who do recover within the 2-week time frame may have the dose reduced to 160 mg for 300-mg dose arm and to 100 mg for 160-mg dose arm.

For Parts C and D: in case of a dose delay of LY2157299, patients can continue sorafenib or ramucirumab treatment (at investigator discretion).

For Part E, patients who do recover within the 2-week time frame may have the dose reduced to 160 mg or their schedule altered after discussion between the investigator and Lilly CRP.

9.5.2. Sorafenib

Doses will be delayed or reduced for clinically significant hematologic and other toxicities (Table JBAK.~~9.4~~7; see Table JBAK.~~9.5~~8 for modifications due to skin toxicity) that are related to sorafenib. In case of a dose delay of sorafenib, patient can continue LY2157299 treatment (at investigator discretion).

Table JBAK.~~9.4.~~7. Sorafenib Dose Modifications for Hematologic and Nonhematologic Toxicities

Grade	Dose Delay	Dose Modification
Hematologic toxicities		
Grade 0-2	Treat on time	No change
Grade 3	Treat on time	Decrease 1 dose level
Grade 4	Delay[a] until ≤ Grade 2	Decrease 1 dose level
Nonhematologic toxicities (except skin toxicity)[b]		
Grade 0-2	Treat on time	No change
Grade 3	Delay[a] until ≤ Grade 2	Decrease 1 dose level[c]
Grade 4	Off protocol therapy	Off protocol therapy

Source: Llovet et al. 2008 supplementary material.

[a] If no recovery after 30-day delay, treatment will be discontinued unless patient is deriving clinical benefit.

[b] Also excludes nausea/vomiting that has not been premedicated, and diarrhea.

[c] If >2 dose reductions are required, treatment will be discontinued.

Table JBAK.~~9.5.~~8. Suggested Sorafenib Dose Modifications for Skin Toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modifications
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet that does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0-1. When resuming treatment, decrease sorafenib dose by 1 dose level (400 mg daily or 400 mg every other day)
	4th occurrence	Discontinue sorafenib treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain	1st or 2nd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0-1. When resuming

of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living		treatment, decrease sorafenib dose by 1 dose level (400 mg daily or 400 mg every other day
	3rd occurrence	Discontinue sorafenib treatment

Source: FDA, 2011 (sorafenib prescribing information).

9.5.3.3. Proteinuria

Monitor for the development or worsening of proteinuria during ramucirumab therapy. If the urine protein level is ≥2+, perform a 24-hour urine collection. Temporarily discontinue ramucirumab administration if the urine protein level is ≥2 g/24 hours. Resume treatment at a reduced dose level (see Table JBAK.9~~.6~~) once the urine protein level returns to <2 g/24 hours. A second dose reduction (see Table JBAK.9~~.6~~) is recommended if a urine protein level ≥2 g/24 hours reoccurs.

Permanently discontinue ramucirumab therapy if the urine protein level is >3 g/24 hours or in the setting of nephrotic syndrome.

Table JBAK~~.9.6.~~.9. Ramucirumab Dose Reductions for Proteinuria

Initial Ramucirumab Dose	First Dose Reduction to:	Second Dose Reduction to:
8 mg/kg	6 mg/kg	5 mg/kg

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing (Standard Laboratory Testing, Pharmacokinetics, Biomarker Analysis), and Appropriateness of Measurements

- **Long-Term Follow-up Period:** All subsequent long-term follow-up visits will occur at 60-day intervals (±7 days) (for example, Visit 802, Visit 803, etc.) until the patient meets the requirements to discontinue from the study. These are the preferred windows for follow-up visits (Visit 802 and beyond); however, if some information cannot be obtained at all or not within the specified window for Visit 802 and beyond, it will not result in a protocol violation if no cardiac toxicity ~~was observed at V801~~ requiring further cardiac monitoring was observed at V801.

10.2.2. Summary of Adverse Event/Serious Adverse Event Reporting Guidelines

Table JBAK.10~~.1~~ presents the reporting schedule for AEs and SAEs.

Table JBAK.~~10.1.~~10. Assessment Guide for Adverse Events and Serious Adverse Events

Timing	Types of AEs/SAEs Reported
Prestudy (Starts at the signing of informed consent and ends at the first dose of study drug)	• Preexisting conditions • All AEs/SAEs (except for patients who do NOT enroll). For enrolled patients, only AEs/SAEs related to protocol procedures should be reported.
On therapy (Starts at first dose of study drug[s] and ends at last dose of study drug[s])	• All AEs and clinically significant lab values regardless of relatedness • All SAEs regardless of relatedness (except death due to progressive disease unless the investigator also deems there to be a possible contribution related to study drug)
Initial follow-up Visit (V801) (Starts at discontinuation from study treatment and ends when end of study safety assessments are completed [30 days, ±3 days, after discontinuation from study treatment])	• All AEs and clinically significant lab values regardless of relatedness • All SAEs regardless of relatedness (except death due to progressive disease unless the investigator also deems there to be a possible relation with study drug)
Subsequent follow-up visits, if necessary	• Ongoing or new AEs/SAEs possibly related to study drug(s) or protocol procedures

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

10.2.4. ~~Echocardiographs~~Echocardiograms with Doppler and Chest CT Scans

Because of the cardiotoxicity monitoring in this study, echocardiographs with Doppler and chest CT scans are being performed (see Attachment 1~~,~~, Attachment 12, and Attachment 13). Echocardiography with Doppler will be locally assessed at screening for enrollment and throughout the study according to the Study Schedule (Attachment 1~~)~~) for safety decisions by a physician or a person who is qualified by experience or training. The individual must be identified at each site. A central reading will be performed for the data used in the study report.

Chest CT scan with contrast of thorax and abdomen to evaluate the large vessels of the heart will be locally assessed at screening for enrollment and throughout the study according to the schedule of events (Attachment 1~~)~~) for safety decisions by a physician or a person who is qualified by experience or training. Alternatively, chest and/or abdomen MRI are allowed.

10.3.2. Samples for Drug Concentration Measurements – Pharmacokinetics/Pharmacodynamics

For Cycles 1 and 2 safety assessments during Part D, PK samples for LY2157299 ~~and~~will be collected on Days 1, 14 and 15, and samples for ramucirumab will be collected on Days 1~~, 14,~~ and 15. One morning PK sample (Day 15 before ramucirumab dosing)~~ will then be taken~~ to evaluate the elimination-phase kinetics of LY2157299 during the nondosing phase of Cycles 1 and 2 ~~(see Attachment 4).~~and one ramucirumab PK sample at end of infusion will be taken. From Cycle 3 onwards, only predose Day 1 samples will be taken.

For Part E, PK samples for LY2157299 will be collected on Days 1, 21 and 22 (Attachment 4).

10.3.3.1. Pharmacogenomic Evaluations

Blood samples will be collected at the times specified in the Study Schedule (Attachment 1). Supplies required for the collection, handling, and shipment of the patients' samples will be provided by the sponsor. Samples will be stored at a facility selected by the sponsor in the ~~United States (~~US~~).~~. Collection of a blood sample for genetic testing is a mandatory part of this study where local regulations allow. The blood sample for pharmacogenomics evaluation will be a 1-time collection unless the sample does not yield adequate DNA for use. It is recommended that the blood sample be taken at the baseline visit but may be taken at any time while the patient is participating in the clinical study. Genes related to safety, efficacy, PK, and/or the mechanism of action of LY2157299 may be tested. Patients will not have the option to request test results and will not receive the genetic test results.

12.1. Determination of Sample Size

The first interim analysis was completed. However, an additional data review was carried out prior to the planned second interim analysis, and this was when 64 patients had received at least 1 dose of study drug and were reported in the clinical database. Of these, 44 patients had completed at least 3 cycles of treatment or discontinued from study treatment. The decision from this review was to stop enrollment into Cohort 1 (at 37 patients) and to complete enrollment of Cohort 2 (n=70 patients). In addition, the protocol was amended (Amendment [b]) to have 2, and possibly 3, parts in this study. The 2 cohorts planned in the original protocol and in the Amendment (a) ~~will be~~were designated as Part A. Part B ~~will~~was to enroll 40 Child-Pugh Class A or B7 patients with HCC with AFP levels<1.5x ULN. Part C ~~will~~was to enroll approximately 40 Child-Pugh ~~A~~B7 or B8 status patients ~~who have not received any prior systemic therapy~~.

The 2 planned interim analyses described for Parts A and B in Amendment (b) have been completed (December 2012 and June 2013).

With Amendment (c), the study planned to enroll approximately 190 patients: 109 patients have been enrolled in Part A (37 in Cohort 1, 72 in Cohort 2~~), and~~); 40 are planned for Part B, and 40 for Part C. ~~With Amendment (d) and the addition of Part D, an additional 15~~ (amended to enroll Child Pugh A patients ~~may~~who had not received any prior systemic therapy and were to be ~~enrolled.~~treated with LY2157299 plus sorafenib in a safety lead-in followed by an expansion at the selected dose).

With Amendment (d) and the addition of Part D, an additional 15 patients may be enrolled. With Amendment (e) and the addition of Part E, approximately 23 additional patients may be enrolled.

The primary objective of the study now is to characterize the TTP distributions, the effect on TGF-β-associated serum biomarkers (for example, TGF-β, AFP, E-cadherin) and the relationship between biomarker response and efficacy endpoints of:

1) Each of the 2 doses of LY2157299 in second-line patients or patients ineligible to receive sorafenib with HCC who have elevated AFP levels (Part A, Cohorts 1 and 2),

2) In second-line patients or patients ineligible to receive sorafenib with HCC who have AFP levels <1.5x ULN dosed at 300 mg/day (Part B),

3) In first-line patients with HCC treated with 2 doses of LY2157299 in combination with sorafenib. If the decision in Part C is to use only 1 treatment group in the expansion cohort, the results from patients at the other dose will simply be listed.

4) In second-line patients with HCC treated with LY2157299 given for 21 days on followed by 7 days off (Part E).

Data from patients from Part D and E will be summarized separately from the data in Parts A, B, and C.

12.2.1. General Considerations

Patients from all sites will be pooled for the purposes of analysis. All confidence intervals of treatment effects will be provided at a 2-sided alpha level of 0.10, unless otherwise stated. Patients with Child-Pugh Class A and B7 will be considered as 1 group of patients, given the similarity of Class B7 patients to Class A patients. If all patients in Part A and Part B are second-line, Part C patients will be analyzed as a separate group. If there are some first-line patients in Part A or Part B, different subgroups may be required. Part D will be conducted outside of the EU. Data from patients from ~~Part~~Parts D and E will be analyzed separately from Parts A, B, ~~and~~ C.

12.2.8. Clinical Efficacy Analyses

Kaplan-Meier analysis will be performed on the observed distribution of TTP (Kaplan and Meier 1958) for each dose in Part A, Part B, Part C, Part D and Part ~~D~~E, with parameter estimates of the TTP median and quartiles being reported. All parameter estimates will be quoted together with their 90% confidence limits. The hazard ratio between the observed TTP distributions of each cohort in Part A will be estimated, recognizing that since 1 dose cohort did not enroll to its full complement, the precision of the HR will be lower than originally planned. The hazard ratios between the 300 mg/day cohort in Part A and Part B cohort will also be estimated. In addition, the hazard ratio between a subgroup of sorafenib-naive patients in Parts A and B and patients in Part C may be estimated. The interpretation of any estimate will be considered in light of the size of this subgroup.

The overall response rate (ORR) for each cohort in Part A, Part B, Part C, Part D and Part ~~D~~E will be estimated by dividing the total number of confirmed responders by the number of patients who received at least 1 dose of study treatment. The clinical benefit rate will be estimated for each treatment group by dividing the total number of patients experiencing benefit by the number of patients who received at least 1 dose of study treatment. A patient is considered to have received benefit if they achieve a confirmed response, CR or PR, or SD per RECIST v1.1 or mRECIST. Both mean and exact confidence limits will be provided for each group (Cohort 1 and Cohort 2 in Part A, Part B, Part C, Part D and Part ~~D~~E, as well as estimates of differences between 2 cohorts in Part A, between Parts A and B at 300 mg/day, and between sorafenib-naive

patients in Part A and Part B with those in Part C. The interpretation of any estimate in the latter comparison will be considered in light of the size of this subgroup.

Additional exploratory analyses of efficacy endpoints will be performed to assess the effect of important prognostic factors on the outcome, including, but not exclusively, baseline AFP levels (either as a continuous factor and/or categorical factor), etiology, and whether sorafenib-~~-~~naïve or not. Analyses using subgroup identification methods, such as classification and regression tree (CART) (classification and regression tool) may also be carried out. The only difference between Part A and Part B patients is their baseline AFP levels, and therefore results from Cohort 2 in Part A and Part B will be combined in these analyses. Similar analyses for patients in Parts C, D and ~~D~~E may be carried out.

The original statistical analysis plan (SAP) was finalized prior to the first patient in the study being dosed. The amended SAP was finalized prior to the first patient in Part B being dosed. The amended SAP (version 2) was finalized prior to the first patient in Part C being dosed. The amended SAP (version 3) will be finalized prior to the first patient in Part D being dosed. An amended SAP (version 4) will be finalised prior to the first patient in Part E being dosed.

12.2.10. Pharmacokinetic/Pharmacodynamic Analyses

For the purposes of the JBAK study report, plasma-concentration data will be illustrated graphically and summarized descriptively. If data ~~is~~are sufficient, then data from patients in this study will be modeled using the population approach for characterizing LY2157299 PK. In addition, if appropriate, data from patients in this study will be combined in a PK database with data from Study JBAH and other completed studies, for population PK analysis. In Part C, Cycle 1 assessment on possible sorafenib exposure change during monotherapy and combination will be made. In Part D, Cycle 1 and 2 assessment of the possible LY2157299 exposure and/or ramucirumab change when in administered in combination ~~with ramucirumab~~ will be evaluated. In Part E, Cycle 1 LY2157299 PK profile of patients dosed for 21 days on treatment and 7 days off treatment will be characterized.

12.2.13. Exploratory Analyses

Given the more limited number of patients to be enrolled in Part D and E, exploratory analyses will be carried out as appropriate.

12.2.14. Interim Analyses

For enrollment to continue in either dose level, there had to be no evidence of cardiotoxicity in any patient at that dose level and no drug-related CTCAE Grade 3/4 toxicity that was not manageable. The PK of LY2157299 in HCC patients were compared to those of patients with glioblastoma observed in Study JBAH. Since only sparse sampling ~~is being~~was performed in ~~this study,~~Study JBAK (Parts A and B), comparisons between the 2 populations were carried out by simulations (median and 20th and 80th percentiles) using the population PK model from Study JBAH.

Enrollment after the first interim analysis continued in both dose cohorts, and a second interim analysis was planned when an additional 30 patients had been enrolled in each arm (~~ie,~~i.e., total

of 40 patients in each arm) and had been actively followed for 3 months or progressive disease or death had been observed. This was to be after the second planned radiological assessment (planned every 6 weeks) and after the collection of biomarker (specifically AFP) samples for all patients. Any patient who was lost to follow-up or started a new anticancer therapy before 3 months had elapsed without an event being observed was not eligible for inclusion in the interim analysis.

Analysis of the mean fold change from baseline of biomarker concentrations levels ~~will~~were to be estimated from a mixed-effects model with sampling time, dose and their interaction as fixed effects, baseline levels (either as a continuous variable or categorical [AFP: ≤400 ng/mL or >400 ng/mL]) as a covariate and patient as a random effect. The choice of variance-covariance structure ~~will depend~~was to have depended on the data. Biomarker concentrations ~~will~~were to be log transformed prior to analysis. Specific details of these analyses will be provided in the SAP.

However, the planned second interim analysis described in Amendment (a) was not carried out~~. The decision to carry out~~, but an additional data review ~~is described in Section 5.1.5.1.~~was conducted. Based on this review, the decision was to close Cohort 1 and continue enrollment until 70 patients ~~have been~~ enrolled ~~in~~into Cohort 2. At the time of the decision, ~~74~~64 patients had been treated.

As part of Amendment (b), the second interim analysis for Part A ~~is now~~ was changed and planned to be after the 70th patient ~~has~~ enrolled into Cohort 2 and started Cycle 1. The purpose of this analysis ~~is~~was to help inform the decision to prepare for further development of the compound in patients with HCC with elevated AFP levels. This analysis was completed in December 2012 (Faivre et al. 2013).

The purpose of the interim analyses in Part B (interim analysis 3) and Part C (interim analysis 4) ~~is~~was to prepare for further development of the compound and to inform the decision as to whether all second-line HCC patients, irrespective of baseline AFP levels~~,~~ (Part B), and ~~all first-line~~ Child-Pugh ~~A~~B7 or ~~B7~~B8 status (Part C) patients may benefit from treatment with LY2157299.

The timing of the interim analyses for Parts B and C ~~is~~was based on assuming Parts B and C are designed as a Simon's 2-stage design with the same characteristics as used in the original protocol: where the assumption of a poor treatment is if the proportion free from disease progression is 50% at 3 months (assumes median TTP = 3 months) and a good treatment is if the proportion free from disease progression at 3 months is 63% (assumes median TTP = 4.5 months). The operating characteristics of this design are as follows: The null hypothesis is that the true response rate is 50%. In the first stage, 18 patients will be accrued and actively followed for at least 3 months or until they have discontinued. If there are 8 or fewer patients free from disease progression in these 18 patients, this may be indicative that patients with normal AFP levels are not benefiting from the treatment. The additional 22 patients will be accrued for a total of 40. The null hypothesis will be 'rejected' at the end of Parts B and C if 22 or more patients out of 40 patients in each part are observed to be free from disease the true response rate is 63%.

From Amendment (c), the above calculations now only ~~apply~~applied to the third interim analysis (for Part B, completed June 2013). Given the change in strategy for Part C~~,~~ to enroll and treat first line Child Pugh A or B7 patients in amendment (c), only safety reviews are planned while the study is ongoing. An additional analysis may be carried out if needed to help with clinical planning of the compound for treating first-line patients.

~~The final analysis for Parts A and B will be conducted after the study objectives for these 2 parts have been met.These analyses will be as described in the SAP and the results will help with the clinical planning of the compound for treating second-line patients.~~

Safety reviews for Part D are planned to determine the LY2157299 dose in combination with ramucirumab. This will be after 3 patients have completed 1 cycle of treatment in Cohort 1 (LY2157299 80 mg BID) prior to escalating to Cohort 2 (LY2157299 150 mg BID). A further safety review will be carried out after 3 patients have completed 1 cycle in Cohort 2.

In Part E, safety data will be reviewed after 3 patients have completed one cycle. If the schedule is deemed to be tolerable (<33% DLTs in Cycle 1 and consideration of the overall safety profile in later cycles), an additional 20 patients will be enrolled in order to better characterize the safety of the schedule and allow comparison to safety, pharmacokinetics and efficacy seen in other cohorts. No additional interim analyses are planned for Part E.

The timing of the final analyses for each study parts' clinical study reports and the final database lock is provided in Section 7.1.

14. References

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Attachment 1. Protocol JBAK Study Schedule

Part E

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	≤28	≤14	≤7	1[i]	8[i]	14[i]	21	22	1[i]	14[i,k]	1[i]	14[i,k]				
Procedures																
Informed Consent	X															Informed consent must be signed prior to performing any study procedures.
Medical History		X														
Child-Pugh, Barcelona Clinic Liver Cancer (BCLC), and CLIP staging			X[h]													
Pregnancy Test			X													
Physical Exam		X		X		X			X	X	X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
Vital Signs (heart rate, blood pressure)		X		X		X			X	X	X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
CTCAE Grading		X		X		X			X	X	X		X	X	X[a]	Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.
DLT Assessment								X								
Concomitant Medications		X		X					X		X		X	X	X	Perform predose on Day 1 of each cycle in extension period.
Performance Status		X		X		X			X	X	X		X	X		Starting in Cycle 3, to be performed once per cycle. Perform predose on Day 1 of each cycle in extension period.

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	**21**	**22**	**1[i]**	**14[i,k]**	**1[i]**	**14i,k**				
Tumor Assessment, Physical (Palpable or Visible)		X		X					X		X			X		Optional during the extension period (including extension period V801)
Imaging Procedures																
Echocardiogram with Doppler[g]	X								X		X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8, etc). Perform predose on Day 1 of each cycle in extension period
Chest CT Scan or Chest MRI		X											X	X[c]		CT scan or MRI every 6 months
Tumor Assessment, Radiological		X								X	X			X[d]	X[d]	Tumor assessment every 6 weeks starting Cycle 2, Day 14. May be performed 3 days around the scheduled date. Optional during the extension period (including extension period V801)
ECG		X							X		X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8, etc). Perform predose on Day 1 of each cycle in extension period

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	≤28	≤14	≤7	1[i]	8[i]	14[i]	21	22	1[i]	14[i, k]	1[i]	14[i, k]				
Laboratory /Diagnostic Tests																
ECG chemistry		X							X		X		X	X[b]	X[b]	Cycle 2, 3, 4, and every other cycle (C6, C8, etc). Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Special chemistry			X		X	X		X	X	X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Hematology			X		X	X		X	X	X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Serum chemistry			X		X	X		X	X	X	X	X	X	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Urinalysis		X							X		X			X		Optional during the extension period (including extension period V801)
Urine C-terminal telopeptides of Type 1 collagen		X							X		X					Optional during the extension period

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	**≤28**	**≤14**	**≤7**	**1[i]**	**8[i]**	**14[i]**	21	**22**	**1[i]**	**14[i], k**	**1[i]**	**14[i], k**				
PK sampling[e]				X			X	X	X		X					Timed with ECG. See Attachment 4 for specific timepoints.
Serum markers (AFP, AFP L3, E-cadherin, PIVKA II)		X		X			X		X		X		AFP only	X		Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Immuno-phenotype				X					X		X			X		Optional during the extension period (including extension period V801)
TGF-β+PF4		X		X			X		X		X			X		Optional during the extension period (including extension period V801)
MAP panel				X			X		X		X			X		Optional during the extension period (including extension period V801)
Fibrotest		X					X		X		X					
aPTT/PT/ INR		X		X					X		X		X			Perform predose on Day 1 of each cycle in extension period. Can be done at local labs during the extension period
Patient-Reported Outcomes																
FACT-Hep		X							X		X			X		Optional during the extension period (including extension period V801)

Cycle/Visit[j]	Prestudy			Cycle 1					Cycle 2		Cycle 3, n[l]		Extension Period	Visit 801	Follow-up[f]	Comments
Relative Day Within a Cycle	≤28	≤14	≧ 7	1[i]	8[i]	14[i]	21	22	1[i]	14[i,k]	1[i]	14[i,k]				
Translational Research																
Whole blood for PGx		X														
Obtained diagnostic tumor tissue, when available		X														
Optional tumor biopsy	X									X						+/- 3 days after end of treatment with LY2157299

Abbreviations: AFP = alpha-fetoprotein; aPTT = activated partial prothrombin time; C = cycle; CLIP = Cancer of the Liver Italian Program; CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = electrocardiogram; FACT = Functional Assessment of Cancer Therapy; INR = international normalized ratio; MAP = multi-analyte panel; MRI = magnetic resonance imaging; PGx = pharmacogenomics; PIVKA II = prothrombin induced by vitamin K absence; PK = pharmacokinetic; PT = prothrombin time; TGF-β = transforming growth factor beta.

a If drug-related toxicity is present 30 days after last cycle of study drug, patients must be followed up approximately every 30 days until toxicity resolution, stabilization, another therapy is initiated, or death.

b If the patient has clinically significant cardiac findings at discontinuation (V801), echocardiography with Doppler, ECG, and ECG chemistry will be repeated every 2 months for 6 months (V803, V804, and V805). If there are no cardiac findings at discontinuation (V801), 1 more echocardiography with Doppler, ECG, and ECG chemistry will be performed after 2 months (V802) unless a patient is receiving another treatment (see Section 10.2.4).

c If there were no clinically significant findings at the last assessment conducted within the 30 days following discontinuation and the patient has started another treatment, Visit 801 CT scan or chest MRI with contrast will not be performed.

d Repeat radiological scans at study discontinuation may be omitted if a patient has objective disease progression or if imaging has been performed in the previous 3 to 6 weeks.

e For details, see Attachment 4. PK sampling will be performed on Cycle 1, with a predose sample on Day 1 of Cycle 2 and all subsequent cycles.

f Follow-up consists of Visit 802 and all subsequent visits (60 days ±7 days). All patients will be followed for OS until study completion.

g Echocardiogram with Doppler can be performed up to 3 days prior to Day 1.

h Child-Pugh, BCLC, and CLIP assessment procedures can be found in Attachment 5, Attachment 6, and Attachment 7, respectively.

i To be performed predose LY2157299.

j A delay at the start of a cycle (Day 1) of no more than 3 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not counted as a protocol violation.

k In extenuating circumstances, the 'on study drug' window is allowable from Day 10 to Day 14.
l Patients on study for more than 1 year (before entering extension phase) only need tests to be performed on Day 1 of each cycle.

Attachment 2. Protocol JBAK Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[b]
Hemoglobin	Total bilirubin
Erythrocyte count (RBC)	Direct bilirubin
Leukocytes (WBC)	Total Protein
Neutrophils, segmented + bands	Alkaline phosphatase
Lymphocytes	LDH
Monocytes	Creatinine kinase (CK)
Eosinophils	ALT/SGPT
Basophils	AST/SGOT
Platelets	Blood urea nitrogen (BUN)
	Creatinine
Immunophenotype[b]	Uric acid
	Calcium
Urinalysis[a]	Glucose, random (nonfasting)
Specific gravity	Albumin
pH	Cholesterol
Protein	Phosphorus
Glucose	Sodium
Ketones	Potassium
Blood	Magnesium
Leukocyte esterase	
	AFP[b]
ECG Chemistry[b]	AFP L3[b]
Lipase	PIVKA II[b]
Thyroid Stimulating Hormone (TSH)	E-cadherin[b]
Tri-iodothyronine (T3)	TGF-β+PF4[b]
Thyroxine (T4)	
Calcium[c]	aPPT/PT/INR[b]
Glucose, random (nonfasting) [c]	
Albumin[c]	Fibrotest[b]
Phosphorus[c]	
Sodium[c]	Urine C-terminal telopeptides of Type 1 Collagen[b]
Potassium[c]	
Magnesium[c]	Serum Pregnancy Test (females only)[a]
Special Chemistry[b]	
Cystatin C	
Troponin I	
BNP	
High-sensitivity C-reactive protein (hs-CRP)	

Abbreviations: AFP = alpha-fetoprotein; ALT = alanine aminotransaminase; aPTT = activated partial prothrombin time; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; ECG = electrocardiogram; INR = international normalized ratio; LDH = Lactate Dehydrogenase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells; PIVKA II = prothrombin induced by vitamin K absence.

a All samples will be discarded within 60 days of validated test results. Validation will occur at the time of initial testing. All these tests will be performed at a local or investigator-designated laboratory, with the exception of immunophenotype.

b All samples will be discarded within 60 days of validated test results. Validation will occur at the time of initial testing. All these tests will be performed at a Lilly-designated laboratory. Tests will be performed at a local laboratory if performed during the treatment extension period.

c Test not performed if both chemistry and ECG chemistry are required. See Attachment 1.

Attachment 4 Protocol JBAK Pharmacokinetic Sampling Instructions

Part D Sampling Schedule

Day	LY2157299 + RAM Dosing Schedule	Pharmacokinetic Sampling Times (LY2157299) plasma	Pharmacokinetic Sampling Times (RAM) serum
Cycle 1 Day 1 (Day at which RAM and LY2157299 are combined)	Both drugs as per Section 9	Predose[a]	Predose[a]
		1.5-3 h after LY2157299 dose	End of RAM infusion
Cycle 1 Day 14[b] (last day of LY2157299 dosing)	LY2157299 as per Section 9	Predose[a]	
		0.5 h after dose	
		2 h after dose	
		3 h after dose	
		6 h after dose	
Cycle 1 Day 15[b]	RAM only as per Section 9	Morning (before RAM is taken)	Predose
Cycle 1 Day 15	RAM only as per Section 9		End of RAM infusion
Cycle 2 Day 1	Both drugs as per Section 9	Predose[a]	Predose[a]
		1.5-3 hours after dose (LY)	End of RAM infusion
Cycle 2, Day 14[b]	LY2157299 as per Section 9	Predose[a]	
		0.5-2 hours	
		3-5 hours	
Cycle 2, Day 15[b]	RAM only as per Section 9	Morning (before RAM is taken)	Predose
Cycle 2 Day 15	RAM only as per Section 9		End of RAM infusion
Cycle 3, Day 1	Both drugs as per Section 9	Predose[a]	Predose[a]
Cycle 4, n, Day 1	Both drugs as per Section 9	Predose[a]	Predose[a]

Abbreviations: h = hour(s); LY = LY2157299; n = cycle number ≥Cycle 4; PK = pharmacokinetic; RAM = ramucirumab.

a The predose sample has to be taken before receiving any LY2157299 or ramucirumab.

b For patients who will have a Day 15 PK sample taken, their evening dose of LY2157299 on Day 14 should be omitted.

Part E Sampling Schedule for LY2157299

Sample Number	Cycle	Day	Sampling Windows for PK
1	1	1	Predose[a]
2	1	1	0.5-2 hours
3	1	21	Predose[a]
4	1	21	0.5-2 hours
5[b]	1	21	3-5 hours
6[b]	1	22	Morning
7	2	1	Predose[a]
8	3 - n	1	Predose[a]

Abbreviation: PK = pharmacokinetic.

a The predose sample should be taken before the patient receives any LY2157299.

b For patients who will have a Day 22 PK sample taken, the evening dose of LY2157299 on Day 21 should be omitted.

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