H9H-MC-JBAS Statistical Analysis Plan Version 2

A Randomized Phase 2 Study of LY2157299 versus LY2157299 - Sorafenib Combination versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma

NCT02178358

Approval Date: 26-Jul-2017

1. Statistical Analysis Plan: H9H-MC-JBAS: A Randomized Phase 2 Study of LY2157299 versus LY2157299 – Sorafenib Combination versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma

LY2157299 monohydrate

Phase 2 study of LY2157299 in patients with hepatocellular carcinoma who have not received prior systemic treatment for advanced disease. Patients will be randomly assigned to 1 of 3 treatment arms: LY2157299, LY2157299 plus sorafenib, or sorafen b plus placebo.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol H9H-MC-JBAS
Phase 2

Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 26-Jul-2017 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Appendix **Page**

3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention.

This version of the SAP (Version 2) was approved prior to the primary database lock. The main changes and rationale for the changes incorporated in Version 2 are as follows:

- Change some analyses from compulsory to optional, e.g. mixed model of time to symptomatic progression for the PRO data
- Delete one criteria in the list of protocol violations in appendix 1: "Timing of visits outside acceptable window", and add one criteria "Patient not withdrawn from LY2157299 if dosing is delayed for >2 weeks for treatment-related AEs"

4. Study Objectives

4.1. Primary Objective

The primary objective is to compare the overall survival (OS) distributions between LY2157299 plus sorafenib therapy and sorafenib plus placebo therapy (control arm) in patients with advanced Hepatocellular carcinoma (HCC) who have not received prior systemic treatment for advanced HCC disease.

4.2. Secondary Objectives

- to estimate the Hazard Ratio (HR) from the OS distributions between LY2157299 monotherapy and sorafenib plus placebo
- to evaluate the safety of LY2157299 as monotherapy and in combination with sorafenib in HCC patients
- to evaluate the population pharmacokinetics (PK) of LY2157299 as monotherapy and in combination with sorafenib
- to characterize other time-to-event distributions, such as time-to-progression (TTP) and progression-free survival (PFS), based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- to estimate antitumor efficacy using objective response rate (ORR, based on RECIST version 1.1 and modified RECIST [mRECIST]) for each treatment arm
- to assess patient-reported outcome (PRO) measures of disease-specific symptoms, time to symptomatic progression, and health-related quality of life questionnaires such as the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ)-30 and QLQ HCC-18 for each treatment arm

4.3. Exploratory Objectives

- to explore 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 TTP, PFS, and ORR by immune response RECIST (irRECIST)
- to explore tumor volume changes of measurable lesions on computed tomography/ magnetic resonance imagings (CT/MRIs) obtained for tumor response as an assessment of treatment effects on biological growth rate
- to explore the relative effects of LY2157299 versus LY2157299 plus sorafenib versus sorafenib plus placebo on antiangiogenesis as assessed by dynamic contrast-enhanced MRI (DCE-MRI) metrics and on tumor cellularity/cell death as assessed by diffusion-weighted MRI (DW-MRI) metrics. These exploratory MRI techniques will

only be performed at clinical sites where the associated MRI center scanner has been qualified prior to patient enrollment by the imaging core laboratory designated by the sponsor.

- to explore fibrosis-related tests, such as fibrotest
- to assess healthcare resource utilization including transfusions and hospitalizations.

5. Study Design

5.1. Summary of Study Design

Study H9H-MC-JBAS (JBAS) is a 3-arm, randomized, multicenter, global (Asia), Phase 2 study of LY2157299 plus sorafenib therapy or LY2157299 monotherapy compared to sorafenib plus LY2157299-matched placebo therapy in patients with metastatic HCC. Patients who receive sorafenib and investigators will be blinded to the LY2157299 or placebo assignment for those arms.

Approximately 120 patients will be randomly assigned in a 1:2:1 fashion to 1 of 3 treatment arms: LY2157299 monotherapy, LY2157299 plus sorafenib 400 mg BID, or sorafenib 400 mg BID plus LY2157299-matched placebo. The monotherapy dose will be 150 mg BID (300-mg daily dose) for 14 days, followed by 14 days with no study drug. The LY2157299 dose used in combination with sorafenib will be 150 mg BID (300-mg daily dose). LY2157299 and matched placebo will be given for 14 days followed by 14 days of rest; sorafenib will be given each day during the cycle. A cycle is defined as 28 days in duration (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.

Patients may receive treatment until they met at least one of the discontinuation criteria (H9H-MC-JBAS Protocol Section 7.3.1).

This Phase 2 study will be considered complete after 100 deaths for OS analysis have occurred. Patients still on treatment at the time that the study is considered complete may enter the treatment extension period and continue with the study treatment (see H9H-MC-JBAS Protocol Section 5.1.1). Patients who are no longer on study treatment at the time of study completion and who have completed at least the 30-day safety follow-up visit (Visit 801) 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.

End of study (trial) is the date of the last visit or last scheduled procedure shown in Protocol Attachment 1 (Study Schedule) for the last active patient in the study. Consult regional standard operating procedures for further information.

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

5.2. Determination of Sample Size

Approximately 150 patients will be entered into this study in order that 120 patients will be randomly assigned to 1 of 3 treatment arms. The randomization will be in a 1:2:1 allocation ratio with 30 patients in LY2157299 monotherapy, 60 patients in LY2157299 plus sorafenib therapy, and 30 patients in sorafenib plus placebo therapy.

The primary objective is to compare the OS distributions between LY2157299 plus sorafenib therapy (combination arm) with sorafenib plus placebo (control arm) using a Bayesian augmented control design. By incorporating historical information regarding the control group into the Bayesian model, it is possible to improve the operating characteristics compared to a standard (frequentist) analysis. The primary objective will be considered to be met if, after 120 patients have completed at least 2 years of follow-up, the posterior probability is >84% that the HR for OS of the combination arm versus control arm is <1.

The study is designed to observe approximately 100 deaths. Simulations (FACTS version 3.2) were carried out using below assumptions:

- Exponential survival model using summary hazard rates from 2 previous sorafenib trials in Asia-Pacific population (see Table JBAS.5.1), along with data from the sorafenib plus placebo arm in this study;

Table JBAS.5.1. Summary of Historical Trials

Trial Name	Sample Size	Median OS (Months)	Hazard Rate (per Week)
Cheng et al. 2009	150	6.5	0.02666
Cheng et al. 2011	410 (Asian Pacific subgroup)	8.8	0.0197
Weighted overall	560	8.2	0.0216

Abbreviation: OS = overall survival.

- A fixed prior distribution for the sorafenib plus placebo hazard rate following a gamma distribution with a mean of 0.0216/week and a weight of 10 (strong prior) and a weight of 1 (weak prior);
- The prior distribution of the log HR between the combination arm and the control arm is assumed to be normally distributed with a mean of 0 and a standard deviation of 100 (weak prior);
- True HRs between the combination arm and the control arm, LY2157299 monotherapy arm and the control arm, are 0.667 and 1, respectively;
- The accrual rate is 10 patients/month (1.7 patients/week);
- The minimum follow-up for the last patient is approximately 2 years (104 weeks).

The simulations indicate that, by randomizing 120 patents, the posterior probability of concluding superiority of the combination arm over the control arm is approximately 83% (strong prior) and 74% (weak prior) (Table JBAS.5.2). Assuming an HR of 1, the posterior probability of concluding superiority of the combination arm over the control arm (that is, type I error) is approximately 14% to 15%. For comparison purpose, a frequentist analysis using the log-rank test would give a power of 73% assuming the HR = 0.667 and type I error = 14% (one-sided).

Table JBAS.5.2. Simulation Results for Final Analysis

N (Deaths)	Control Rate Prior	Timing of Analysis	Type I Error	Posterior Probability (HR <1) > 0.84
120 (100)	Strong prior for final analysis	FPV + 32.7 months	14%	83%
120 (100)	Weak prior for final analysis	FPV + 32.7 months	15%	74%

Abbreviations: FPV = first patient visit; HR = hazard ratio.

5.3. Method of Assignment to Treatment

For this study, approximately 120 patients with advanced HCC who have not received prior systemic treatment and who meet all criteria for enrolment will be randomly assigned by the interactive web-response system (IWRS) to receive LY2157299 monotherapy, LY2157299 plus sorafenib, or sorafenib plus LY2157299-matched placebo in a 1:2:1 ratio after completing the screening at Visit 0. Additionally, patients who receive sorafenib and investigators will be blinded to the LY2157299 or placebo assignment for those arms (Arms 2 and 3).

A dynamic allocation method, introduced by Pocock and Simon (1975) (and extended for unequal treatment group sizes by Han et al. [2009]), will be adopted to minimize imbalance between treatment arms according to the following factors:

- AFP (>200 ng/mL vs ≤200 ng/mL)
- portal vein thrombosis (yes vs no)

The randomization parameter P will be set at 0.9 to maximize the benefit of the allocation procedure while keeping treatment assignments unpredictable. Randomization will be monitored periodically, and the randomization parameter will be modified if necessary.

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

The IWRS will be used to assign blister packs containing study drug to each patient. Site personnel will confirm that they have located the correct blister packs by entering a confirmation number found on the blister packs into the IWRS.

6. A Priori Statistical Methods

6.1. General Considerations

This plan describes a priori statistical analyses for efficacy and safety that will be performed according to Protocol version 1.0 dated November 18, 2013. Additional exploratory analyses of the data not described in this plan will be conducted as deemed appropriate.

Statistical analysis of this study will be responsibility of both Quintiles (under the direction of Eli Lilly and Company [Lilly]) and Lilly.

The interpretation of the study results will be the responsibility of the investigator with the Lilly Clinical Research Physician (CRP), pharmacokineticist, and statistician.

Patients from all sites will be pooled for the purposes of analysis. Inference about survival will be made using a Bayesian posterior probability for the superiority of LY2157299 plus sorafenib arm survival over sorafenib plus placebo arm. The remaining analyses of this study will estimate differences between arms where appropriate, including exploratory analyses. Descriptive statistics by treatment arm will also be provided.

Results of descriptive analyses and estimates from inferential analyses will be presented by treatment arm. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Any missing longitudinal data will not be imputed, but rather will be estimated from an appropriate random mixed-effects model. Transformations will be applied where assumptions behind any analysis are better satisfied by data being transformed onto an alternative scale. All results from any of these analyses will be back transformed to the original scale. Alternatively, nonparametric methods will be applied.

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.

The following terms and data handling conventions defined in Table JBAS.6.1 will be used in the analysis.

Table JBAS.6.1. Data Handling Conventions

Term	Definitions or Rule
Entered	Patients who have signed the informed consent document directly.
Screen failures	Patients who have signed informed consent, do not meet eligibility criteria and are not treated/randomized.
Randomized	Patients who have been assigned to study treatment but may have not received any study treatment (LY2157299, LY2157299-matched placebo, or sorafenib).
Patients on therapy	Patients who have been randomized to study treatment and have received at least 1 dose of study treatment (LY2157299, LY2157299-matched placebo, or sorafenib).

Study day	If assessment is on or after date of first treatment dose then
	(date of assessment) – (date of first study treatment dose) + 1
	If assessment precedes first treatment dose then
	(date of assessment) – (date of first study treatment dose)
	There is no study day 0. Study day 1 is the date of first dose and study day -1 is the day before the first dose.

Cycle day	If assessment is on or after date of first treatment dose then
	(date of assessment) – (date of first study treatment dose in cycle) + 1
	If assessment precedes first treatment dose then
	(date of assessment) – (date of first study treatment dose in cycle)
	There is no cycle day 0. Cycle day 1 is the date of first dose in the cycle and cycle day -1 is the day before the first dose.

Baseline	For change from baseline analysis, baseline value is defined as the last reported measure on or before the first dose date (or discontinuation, if no treatment is given). For change from baseline within a cycle, the measure prior to the first dose if that cycle is baseline.
Study treatment period	Time from treatment start to discontinuation from study treatment
Post-discontinuation – short-term follow-up	The short term follow-up period begins 1 day after discontinuation of study treatment and lasts approximately 30 days (Visit 801).
Post-discontinuation – long-term follow-up	The long-term follow-up period begins 1 day after the short-term follow-up period (Visit 801) is completed and continues until death to collect survival data.

6.1.1. Analysis Populations

The following populations used for analysis are defined in Table JBAS.6.2 below.

Table JBAS.6.2. Populations used for Analysis

Population	Definitions or Rule
Randomized	Patients who have been randomized to study treatment. Patients in this set will be grouped according to their allocated treatment. All subject characteristics and efficacy analyses (except tumor response) will be conducted on this population.
Per-protocol	Patients who have been randomized to study treatment and did not have any major protocol deviations. Patients in this set will be grouped according to their allocated treatment. Efficacy analyses might be conducted on this population in addition to the randomized population.
Tumor response qualified	Patients who have been randomized to study treatment, received at least 1 dose of study treatment (LY2157299, LY2157299-matched placebo, or sorafenib), had measurable disease at baseline and had at least one baseline and one study treatment period tumor assessment. Tumor response analyses (Section 6.9.2.2) will be conducted on this population. Patients in this set will be grouped according to their allocated treatment, and then the analysis will be repeated using the actual treatment assignment.
Safety	Patients who have been randomized to study treatment and have received at least 1 dose of study treatment (LY2157299, LY2157299-matched placebo, or sorafenib). Patients will be grouped according to actual treatment received in Cycle 1. Safety analyses and efficacy analyses as specified in Section 6.9.2.1 will be performed on this population.

6.2. Adjustments for Covariates

Additional exploratory analyses may be performed on efficacy measures to adjust for factors that may affect survival or disease progression. See Section 6.9.2.1 on the covariates that will be considered in the survival models.

6.3. Handling of Dropouts or Missing Data

For time-to-event analysis, all censored data will be accounted for using appropriate statistical methods. See Section 6.9 for details. For health outcome analysis, see Section 6.10 for details. For PK/Pharmacodynamic analysis, see Section 6.11 for details.

6.4. Multiple Comparisons/Multiplicity for Primary Endpoint

No adjustment for multiplicity is planned for this study since the primary analysis comparing the OS distributions for only LY2157299 plus sorafenib and placebo plus sorafenib is Bayesian. Other analyses to compare OS between other treatment arms will be secondary or exploratory in nature.

6.5. Patient Disposition

All patient discontinuation from study treatment and study will be documented, and the extent of each patient's participation in the study will be reported. Reason for their discontinuation from both study treatment and study will be listed and summarized by pre-determined categories. The study will be considered complete after 100 deaths have occurred, but patients may continue to receive study drug if they are still benefiting from treatment (see Section 5.1). If known, unique

reason for discontinuation will also be listed. If reason for discontinuation is due to an adverse event (AE) or death, the associated AE or cause of death will be reported.

A listing of patients with identified protocol violations, including patients who did not meet inclusion/exclusion criteria, did not sign informed consent document at visit 0 and who discontinued due to protocol violations, will be provided. See SAP Appendix 1 for a list of potential protocol violations.

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

6.6. Patient Characteristics

6.6.1. Patient Demographics and Baseline Disease Characteristics

Patient demographics, alcohol and tobacco consumption habits, and baseline disease characteristics will be listed and summarized with descriptive statistics for all enrolled patients.

Patient demographics will include a summary of sex, race (including Asian race sub-categories), age, height and weight.

Special instructions regarding presentation of race in summary tables: patient may select more than one of the values for Race and Race Subcategory in the electronic case report form (eCRF). Derive Race and Race Subcategory to 'Multiple' if more than one race or race subcategory is selected. Otherwise, race/race subcategory equals the single race selected. For example, if a patient selects both 'White' and 'Asian' then RACE = 'Multiple'. However, if a patient selects only 'Asian' then RACE = 'Asian'. Similarly, if a patient selects both 'Chinese' and 'Taiwanese' then RACE_SUB = 'Multiple'. However, if a patient selects only 'Chinese' then RACE_SUB = 'Chinese'.

Data listings will list all races and race subcategories as follows: Patients with multiple races will be displayed as 'Mulitple: <Race 1>, <Race 2>, <etc.>' and similarly multiple race categories will be displayed as 'Multiple: <Subcategory 1>, <Subcategory 2>, <etc.>'. For example, RACE = 'Multiple: White, Asian' or RACE_SUB = 'Multiple: Chinese, Taiwanese'.

Alcohol and tobacco consumption habits including the number of drinks consumed per week and smoking status will be summarized and listed.

Baseline disease characteristics will include a listing and summary of Child-Pugh Liver Classification (CPLC) including bilirubin (mg/dL) category, albumin (g/dL) category, ascites, encephalopathy, prothrombin time in seconds prolonged, %, or INR., bilirubin (mg/dL) in cases of biliary cirrhosis; Cancer of the Liver Italian Program Staging System (CLIP) including Child-Pugh, tumor morphology, alpha-fetoprotein category (<400 ng/mL, ≥400 ng/ML), portal vein thrombosis (yes/no); Barcelona Clinic Liver Cancer (BCLC) classification; and baseline ECOG. Alpha-fetoprotein category of ≤200 ng/mL or >200 ng/mL (used as a balancing factor) based on

baseline laboratory data will be included in this listing. Information regarding the diagnosis information will be listed and summarized. Diagnosis information may include the basis of determination for the initial pathological diagnosis (for example, histopathological, cytological, biochemical assay, or imaging), initial diagnosis date, disease stage at study entry, and diagnosis date at study entry.

Disease etiology categories such as HBV/HCV infection and alcohol use will be summarized and listed.

6.6.2. Medical History and Ongoing Pre-existing Conditions

Medical history (MH) conditions are historical illnesses, pre-existing conditions and relevant surgeries or other procedures that started prior to signing the informed consent document. All MH conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (MedDRA Version 16.0 or higher) and by using the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 (or higher).

A **historical condition** is a MH condition that has ended prior to the date of informed consent.

A **preexisting condition** is a MH condition that is either ongoing or has ended on or after the date of informed consent.

Historical and preexisting conditions will be summarized and listed for all randomized patients. Summaries will be presented by System Organ Class (SOC) and by decreasing frequency of MedDRA Preferred Term (PT) within SOC.

The medical history verbatim and MedDRA PT will be listed along with start and end dates. Additionally, CTCAE severity grades will be listed for ongoing pre-existing conditions.

6.6.3. Prior and Post Discontinuation Therapies

All prior therapies performed for HCC, including surgical, radiotherapy (for this cancer), and locoregional will be listed separately for all patients on study therapy. The listing of prior surgical procedures will include date of surgery and the procedure. For prior radiotherapy listing, treatment start and stop date, dose, reason for regimen, and irradiated location will be included. The type of procedure used and the start and stop dates of the procedure will be reported in the listing of locoregional treatments.

Any post therapies following discontinuation will also be listed. This includes systemic therapies in addition to the therapies described above. The listing for post systemic therapies will include the treatment received and treatment start date. Combination systemic therapies will be linked through same regimen number.

Combination of surgical therapy, radiotherapy and/or locoregional treatments will be linked through overlapping treatment period. Alternatively these may be identified by an indicator variable on the CRF, if collected.

The number of patients who had at least one prior therapy and the type of therapy and the number of patients who had at least one post therapy and the type of therapy will be summarized for all patients on study therapy.

6.7. Treatment Compliance

Subject compliance with study medication will be assessed by reconciling the number of tablets of each tablet strength dispensed at the beginning (or during in the event of a prescribed dose reduction) of each cycle with the number of tablets of each strength returned at the end of the cycle. This will be compared with the number of days for each prescribed dose in the visit interval (exposure days). The number of tablets of each tablet strength taken relative to the number expected/planned to be taken will be summarised for each cycle and overall for each patient.

Details of how treatment compliance summaries are created are listed in Section 6.12.1.

6.8. Concomitant Therapy

All medications entered on the CRF will be coded centrally and manually to the World Health Organization (WHO) preferred trade name and WHO drug preferred term (which will still contain some trade names) according to the current WHO drug dictionary. These two terms will be provided in study data tabulation model (SDTM) datasets and form the basis of enabling anatomical therapeutic chemical (ATC) levels to be programmatically mapped from the WHO drug preferred term. Anatomical therapeutic chemical levels chosen will consider both the AE associated with the concomitant medication and intention for use (IFU), as listed on the CRFs. These will be confirmed with the study physician prior to summarizing the data.

Prior medications are medications that ended prior to the first dose of study medication. These medications are discussed in Section 6.6.3, Prior and Post Discontinuation Therapies.

Concomitant medications will be listed for all randomized patients. The WHO preferred term, start and end dates, and indication for which the medication was taken will be listed.

Concomitant medications will be summarized by treatment group for each appropriate ATC level for the drug and WHO preferred term within ATC level for the safety population. A unique count of patients for each ATC level will be provided and if a subject has multiple instances of the same WHO drug preferred term, the subject will be counted only once in the summary table.

Radiotherapy received on study will be listed separately. The listing will be similar to the prior and post discontinuation listings discussed in Section 6.6.3.

6.9. Efficacy Analyses

The following are definitions of the primary and secondary efficacy endpoints:

Primary Endpoint:

- **Overall Survival (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 will be censored for that analysis at the date of last contact prior to the data inclusion cutoff date (contacts considered in the determination of last contact date AE date, lesion assessment date, visit date, and last known alive date).

Secondary Endpoints:

- **Time to Progression (TTP) duration** is measured from the date of randomization to the first date of objective progression of disease based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 prior to the start of any post-discontinuation anti-cancer therapy. For each patient who is not known to have had a progression of disease as of the data-inclusion cut-off date, date of death, or date of initiating any post-discontinuation therapy, time to progression will be censored for that analysis at the date of the patient's last tumor assessment prior to that date.
- **Time to Progression rate at 3 months, 6 months, 9 months, 12 months** is defined as the proportion of patients not having objective progression (based on RECIST version 1.1) at 3, 6, 9, and 12 months respectively after the time from date of randomization estimated from the TTP distribution.
- **Progression-Free Survival (PFS) duration** is measured from the date of randomization to the date of first observation of objective progression (based on RECIST version 1.1) or death from any cause, prior to the start of any post-discontinuation anti-cancer therapy, whichever occurs first. For patients who are not known to have died or progressed as of the data-inclusion cut-off date or as of the date of post-discontinuation anti-cancer therapy, PFS time will be censored at the date of the last tumor assessment prior to that date.
- **Progression-Free Survival rate at 3 months, 6 months, 9 months, 12 months** is defined as the proportion of patients not having objective progression (based on RECIST version 1.1) or death at 3, 6, 9, 12 months respectively after the time from date of randomization estimated from the PFS distribution.
- **Overall Response Rate (ORR)** is defined as the proportion of patients who achieved a best overall response of either complete response (CR) or partial response (PR). The overall response rate for each treatment group will be estimated by dividing the total number of responders by the number of patients qualifying for the tumor response qualified population (Section 6.11). Response will be evaluated based on the RECIST version 1.1 and mRECIST criteria. No confirmation of response is required. Overall response rate will be calculated separately for each evaluation criteria.
- **Disease Control Rate (DCR)** is defined as the proportion of patients who achieved a best response of CR, PR or stable disease (SD). This rate will be estimated for each treatment group by dividing the total number of patients that had CR, PR or SD by the number of patients qualifying for the tumor response qualified population (Section 6.1.1). Best response of SD is defined as disease that does not meet the criteria for CR, PR, or progressive disease (PD) and has been evaluated at least one time, and at least 6 weeks after

baseline assessment. Patients without a valid response assessment at least 6 weeks after baseline assessment are assigned a best response of nonevaluable unless progression has already occurred. Response will be evaluated based on the RECIST version 1.1 and mRECIST criteria. Disease Control Rate will be calculated separately for each evaluation criteria.

All time-to-event endpoints will be analyzed using the Kaplan-Meier method. Covariates may also be included in these time-to-event models to account for variation in survival time. A Bayesian model will be used to estimate the hazard ratio of overall survival between the treatment arms.

Table JBAS.6.3. An Overview of the Efficacy Analyses

Efficacy Endpoint	Statistical Analysis	SAS Procedures
Primary analysis:		
Overall survival (OS)	A Bayesian OS model to estimate the hazard ratio (HR) of OS (under strong prior) and 90% predictive interval between LY2157299 plus sorafenib therapy and sorafenib plus placebo therapy	Non SAS - FACTS
Secondary analyses:		
Overall survival	The same Baysian OS model in the primary analysis will be repeated using a weak prior.	Non SAS - FACTS
	The same Bayesian OS model in the primary analysis is used in secondary analysis to estimate the HR between LY2157299 monotherapy and sorafenib plus placebo therapy	Non SAS - FACTS
	Kaplan-Meier method will be used to estimate median survival time, OS rate at 6 and 12 months, and its 95% confidence interval (CI) for the treatment arms	LIFETEST
	Proportional hazard model will be used to estimate the hazard ratio of survival and 95% CI between treatment arms	PHREG
	Proportional hazard model will be used to estimate the hazard ratio of survival and 95% CI between treatment arms, controlled for other factors. (Note: Use stepwise methods, slentry and slexit criteria)	PHREG
Time to Progression (TTP)	Kaplan-Meier method will be used to estimate median TTP, TTP rates at 3, 6, 9, and 12 months, and its 95% CI for the treatment arms	LIFETEST
	Proportional hazard model will be used to estimate the hazard rate and HR of TTP and 95% CI of the 3 treatment arms and between the treatment arms	PHREG
Progression-free survival (PFS)	Kaplan-Meier method will be used to estimate median PFS, PFS rates at 3, 6, 9, and 12 months, and its 95% CI for the treatment arms	LIFETEST
	Proportional hazard model will be used to estimate the hazard rate and ratio of PFS and 95% CI of the 3 treatment arms and between the treatment arms	PHREG
Overall response rate (CR or PR) Disease control rate (CR, PR or SD)	The overall response rate will be estimated from dividing the total number of responders (CR or PR) by the number of patients qualifying for tumor response qualified population defined in Section 6.1.1. The disease control rate will be estimated from dividing the total number of patients with CR, PR or SD by the number of patients qualifying for tumor response qualified population defined in Section 6.1.1. The exact 95% CI for ORR and disease control rate will also be provided for each arm	FREQ

6.9.1. Primary Outcome and Primary Methodology

A method of analysis for comparing OS between the treatment arms will use a Bayesian exponential-likelihood model on treatment effects. The model incorporates historical data from 2 studies with a sorafenib plus placebo arm to augment the prospective control arm data. If the Bayesian posterior probability of superiority of the combination arm (LY2157299 plus sorafenib) over the control arm (sorafenib plus placebo) (that is, HR <1) exceeds 0.84 under a strong prior, then it will be concluded that the combination arm is superior.

6.9.2. Secondary Efficacy Analyses/Outcomes/Comparisons

6.9.2.1. Additional Analyses of the Primary Outcome

The same Bayesian analysis as described in Section 6.9.1 will be repeated using the weak prior. The same Bayesian analysis will also be carried out to provide the hazard rates and ratios including 90% predictive intervals of the HR between LY2157299 monotherapy and sorafenib plus placebo therapy.

In addition to the above primary Bayesian analyses for OS, OS curves for each treatment arm will also be analyzed using the Kaplan-Meier product-limit method (Kaplan and Meier 1958). Two-sided, 95% CIs for median OS will be computed by the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). OS rates at 6 and 12 months will also be estimated using Kaplan-Meier estimates on the OS curve for each treatment arm. Associated 2-sided 95% CIs will also be calculated. Kaplan Meier plots of survival for each treatment group will also be provided.

Pairwise HRs along with 95% CIs between the 3 arms will be estimated using a stratified univariate proportional hazards (PH) model. Additional exploratory analyses using a PH model to control for other factors may be performed, including, but not limited to, ECOG performance status, portal vein thrombosis (yes vs. no), extra hepatic spread (yes vs. no), baseline AFP levels (<200 vs. ≥200, <400 vs. ≥400), etiology and TGF-β levels (<3400 pg/ml vs. ≥3400 pg/ml). A stepwise procedure for variable selection will be applied. The univariate and multivariate analyses using PH models will be repeated on the safety population (Section 6.1.1) to explore the actual drug effect.

6.9.2.2. Efficacy Analyses of the Secondary Outcomes

Investigator-determined TTP, PFS and TTP/PFS rates will be summarized (at 3 months, 6 months, 9 months, 12 months) using Kaplan-Meier estimates of the median survival times (including 95% CIs). Pairwise HRs along with 95% CIs between the 3 arms will also be provided using stratified PH models. Additional exploratory analyses using PH models to control for other factors may be performed.

Investigator-determined ORR based on RECIST version 1.1 and mRECIST criteria will be estimated by dividing the total number of responders (complete response [CR] or partial response [PR]) by the number of who received at least 1 dose of study treatment and had measureable disease at baseline. Exact 95% CIs by the method of Clopper and Pearson (Clopper and Pearson 1934) for each treatment arm will be provided.

Investigator-determined response (using RECIST version 1.1 and mRECIST criteria) will be listed by patient and cycle. Tumor measurements by patient, cycle, and lesion will be listed. A separate listing will include changes from baseline in the sum of tumor measurements (over all lesions) and clinical assessments by patient and cycle. Efficacy parameters (OS, TTP, best overall response [BOR], minimum percent change from baseline of sum of lesion measurements) will be listed by patient. Additionally, a listing of disease status at the end of the study will be provided.

The listings and summary described above for investigator-determined assessments will be repeated for central readers' assessments when data are available.

All analysis described in this section will be conducted using the Tumor Response Qualified Population grouped based on randomized treatment assignment and repeated using the actual treatment (Section 6.1.1).

6.10. Health Outcomes/Quality-of-Life Analyses

The assessment of PROs, including disease-specific symptoms and health-related quality of life, will be assessed using the EORTC QLQ-30 and QLQ HCC-18.

The EORTC QLQ-C30 is a general measure of quality of life in cancer patients (Aaronson et al. 1993). It is a self-reported instrument consisting of 30 items covered by 1 of 3 dimensions: Global health status/quality of life (2 items); functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning); symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact).

To assess disease-specific symptoms of HCC patients, the HCC-specific module (EORTC QLQ HCC-18) will be used. The EORTC QLQ HCC-18 is an 18-item HCC-specific supplemental module developed to augment QLQ-C30 and to enhance the sensitivity and specificity of HCC-related QOL issues (Blazeby et al. 2004).

Both the EORTC QLQ-30 and QLQ HCC-18 will be administered at baseline, at every cycle starting from Cycle 2, and at discontinuation (Visit 801).

Summary descriptive statistics will be provided for the PRO data (that is, EORTC QLQ-C30 and QLQ HCC-18) at each assessment. This summary will include mean, standard deviation, median, minimum, and maximum. Composite scores for each dimension and total scores will be evaluated in aggregate (that is, median values for each study arm at a given time point) and average change from baseline will be reported for each arm at each time point. Time to symptomatic progression may also be evaluated, and longitudinal analyses, such as repeated measures, may be performed. Other exploratory longitudinal analyses may be performed.

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic and PK/pharmacodynamic analyses are the responsibility of the PK scientist. The following sections are for information only. Detailed plans will be in the PK/pharmacodynamic analysis plan.

6.11.1. Pharmacokinetic Methods

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. Sorafenib PK will be assessed against a published sorafenib population PK model.

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 will 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 JBAS CSR, plasma-concentration data will be illustrated graphically and summarized descriptively. If data is sufficient, then data from patients in this study will be modeled using the population approach for characterizing LY2157299 PK.

Exploratory PK/pharmacodynamic analyses will be conducted to identify the exposure-response (biomarker) relationship in this study. The PK and PK/pharmacodynamic 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 for software validation. It is possible that other validated equivalent PK software programs may be used if appropriate, warranted, and approved by global PK management.

6.11.2. Pharmacodynamic Methods

Pharmacodynamic parameters (for example, E-cadherin, pSMAD, TGF-β1, AFP) will be analyzed using pharmacodynamic data from all patients who underwent PD assessments. The association between changes in PD parameters and clinical endpoints will be explored to determine their value as predictive biomarkers of drug effect on overall survival. These analyses will include creating and using two indicator variables to sub-group patients who have at least a 20% reduction from baseline in AFP and TGF-β1 levels respectively. Exploratory analyses to identify optimal cutoff points for these two variables may be carried out. The relative day of when 20% reduction (if occurs) in each of these biomarkers for each patient will be derived and summary statistics of the distribution provided, in order to understand when it is likely when a pharmacodynamic effect might occur to aid further development.

Additional exploratory analyses may be carried out dependent upon results from other studies using LY2157299.

Details of all these analyses will be provided in the Table, Figure, Listing (TFL) shells.

6.12. Safety Analyses

6.12.1. Treatment Compliance and Dose Intensity

The assigned dose of LY2157299 (or matched placebo) for every patient is 300 mg/day and the assigned dose for sorafenib is 800 mg/day for all patients in the combination arms. A prescribed dose is the dose the patient is prescribed to take in each cycle, including adjustments due to dose reductions or omissions within a cycle if prescribed by the investigator.

Treatment compliance is defined by the patient taking the study drug in mg as prescribed.

Dose intensity is expressed as a percentage of actual daily dose (mg) divided by assigned daily dose (mg) across all cycles, including the last cycle that may have been less than 28 days.

Treatment compliance and intensity information for LY2157299 (or placebo) will use collected pill counts of each tablet strength (150 mg and/or 80 mg if dose is reduced) at each cycle and the date of first dose and date of last dose in every cycle and study treatment discontinuation date. The pill counts will determine the extent of patient exposure to study drug. Similarly, treatment compliance and intensity information for sorafenib will use collected pill counts (tablet strength of 200 mg).

6.12.1.1. Planned dosing

Patients will be randomly assigned to one of the following arms shown in Table JBAS.6.4.

Table JBAS.6.4. Treatment Regimens

	Daily Dose	Schedule	Time of Day	Number of Tablets Prescribed per Cycle[d]
Arm 1	150 mg BID LY	Daily 14 days on/14 days off	Morning and evening for 14 days[a,b] and then paused for 14 days	27 (Cycle 1) 28 (Cycle 2+)
Arm 2	150 mg BID LY[c] plus	Daily 14 days on/14 days off	Morning and evening for 14 days[a,b] with sorafenib and then paused for 14 days.	27 (Cycle 1) 28 (Cycle 2+)
	400 mg (2x200mg) BID sorafenib	Daily	Take in the morning and evening for 28 days	111 (Cycle 1) 112 (Cycle 2+)
Arm 3	LY-matched placebo plus	Daily 14 days on/14 days off	Morning and evening for 14 days[a,b] with sorafenib and then paused for 14 days.	27 (Cycle 1) 28 (Cycle 2+)
	400 mg (2x200mg) BID sorafenib	Daily	Take in the morning and evening for 28 days	111 (Cycle 1) 112 (Cycle 2+)

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.

[a] In extenuating circumstances, the "on-study-drug" window for LY2157299 is allowable from Day 10 to Day 14.

[b] Both study drugs should be taken on an empty stomach, at least 1 hour before a meal.

[c] LY2157299 dose will be defined based on the results of the H9H-MC-JBAK study. Dose will either be 80 or 150 mg BID.

[d] Assuming no prescribed omissions or adjustments.

LY2157299 300 mg/day will be administered orally 150 mg BID in 150–mg tablet form (300 mg total daily dose). A cycle (28 days) will be defined as an intermittent dosing regimen of 14 days of LY2157299 followed by 14 days without LY2157299 administration. All patients should not receive more than 14 consecutive days of LY2157299 dosing (28 tablets).

Sorafenib 800 mg/day will be administered orally 400 mg BID (2 tablets × 200mg BID) for a 800 mg total daily dose. Sorafenib dosing will occur consistently throughout the 28-day cycle. All patients assigned to the combination arms should not receive more than 28 consecutive days of sorafenib dosing (112 tablets).

During Cycle 1 only, all patients should omit the Day 14 evening dose to ensure a 24-hour PK assessment. Visit/cycle start dates may vary ±3 days due to holidays, inclement weather, etc.

Planned dose adjustments and delays

If a toxicity related to LY2157299 is observed, the patient may be prescribed to omit one or more doses or have their dose reduced to 80 mg BID within the cycle. If this occurs, the patient may continue the next cycle on the full assigned dose (300 mg/day). However, if a patient experiences any of the events described in Section 9.4.1.1 of the Protocol, LY2157299 (or

placebo) will be omitted until the event resolves. If dosing is resumed, either in the same cycle or at the start of the next cycle, it will continue at a reduced dose of 80 mg BID (160-mg total daily dose). In case of a dose delay of LY2157299, patients can continue sorafenib treatment (at the investigator's discretion).

Clinically significant toxicities related to sorafenib described in Section 9.4.1.2 of the Protocol will result in dose delays or reductions**.** When dose reduction is necessary, sorafenib dosage may be reduced using the predefined dose levels:

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

At the discretion of the investigator, the sorafenib dose may be reescalated to the previous dose level 400 mg BID after the resolution of the AE.

In case of a dose omission/delay of sorafenib, patients can continue LY2157299 or placebo treatment up to total of 14 days (at the investigator's discretion). In case of discontinuation of sorafenib treatment, patients can still revive LY2157299 or placebo as per protocol (at the investigator's discretion).

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

6.12.1.2. Data Collection Process

Exposure days and prescribed dose

The first dose of Cycle 1 is recorded on the Study Treatment PK - Cycle 1 Day 1 Dose 1 CRFs (EX1001_F1 and EX1001_F16 for LY2157299/Placebo and sorafenib, respectively). The first dose for Cycles 2+ is recorded on the Study Treatment PK - Day 1 CRFs (EX1001_F6 and EX1001_F15 for LY2157299/Placebo and sorafenib, respectively). These forms contain the start date and time, whether the start of the cycle was delayed (Cycles 2+), dose per administration, and dose frequency for each cycle. If there is a dose reduction, the end date and time on the Study Treatment Changes CRFs (EX1001_F7 and EX1001_F13) will reflect the last dosing date/time at the original prescribed dose (for example, the last day the patient took 300 mg/day of LY2157299). The site then enters the new start date and time which will be the day the patient started at the reduced dose (for example, 160 mg/day of LY2157299). If there is a dose omission (whether prescribed or due to patient non-compliance), the start and end dates and times of the missed doses will be recorded on the Exposure Dose Omission CRFs (EX1001_F25 and EX1001_F24). Finally, the Study Treatment Last Dose CRFs (EX1001_F2 and EX1001_F34) will contain the date/time, dose and frequency of the last day in the cycle that the subject took their prescribed dose (for example, if LY2157299 was reduced, 160 mg/day).

Pill counts

At the end of each cycle and the beginning of the next cycle, the number of tablets dispensed and returned of each tablet strength (150mg and/or 80mg tablets for LY2157299 or 200mg tablets for sorafenib) will be recorded on the Study Treatment Compliance CRFs (DA1001_F1 and DA1001_F2).

6.12.1.3. Derivations

Subject compliance with study medication will be assessed by reconciling the number of tablets of each tablet strength dispensed at each cycle with the number of tablets of each strength returned at each subsequent cycle through the end of the study treatment. The number of tablets of each strength will be multiplied by the tablet strength to give the **actual total drug taken** in mg. (Note: This amount could alternatively be derived by taking the sum of the actual days dosing occurred (subtracting omitted days from the dosing interval) multiplied by the actual dose per administration and frequency in each dosing interval). This will be compared with the **prescribed total drug taken** by calculating the number of tablets of each strength expected to be taken (prescribed tablets) multiplied by their tablet strength. The prescribed total dose is based on the days for each prescribed daily dose in the dosing interval (exposure days), accounting for any prescribed dose adjustments (delays, omissions, or reductions). The total drug taken relative to the total prescribed will be summarised for each cycle and overall for each patient. A patient will be considered compliant with the study therapy protocol if the total drug taken indicates the patient took between 80% and 120% of the planned LY2157299 dose in mg during the cycle of study therapy.

Dose intensity takes the total drug taken (mg) (from above) in the study divided by the number of days on study treatment (that is, **average actual daily total** in mg) compared to **the assigned total drug** (mg) divided by the **expected number of days on study**, and expressed as a percentage. The assigned total drug is calculated from the sum of the number of cycles completed times the expected number of days of dosing in each cycle (for example, for LY2157299, 13.5 for cycle 1, 14 for every other completed cycle and the number of exposure days of the last cycle on treatment) multiplied by the assigned daily dose at Cycle 1 (for example, for LY2157299, 300 mg). The expected number of days from first dose to study treatment discontinuation is the number of cycles completed times 28 (the expected cycle length) plus the number of days prior to study treatment discontinuation in the last cycle. Dividing assigned total dose by the expected number of days prior to study treatment discontinuation gives the expected daily dose in mg. This calculation allows for dose delays.

The dose intensity per patient will be summarised using descriptive statistics.

The following compliance and dose intensity definitions (Table JBAS.6.5) will be used to calculate compliance and intensity for each cycle and overall for each patient:

Table JBAS.6.5. Compliance and Dose Intensity Definitions

Term	Definitions or Rule
Compliance rate (%)	100 x actual drug taken (mg) / total drug (mg) prescribed Calculated for each cycle and overall for each patient
Dose Intensity (%)	100 x actual daily dose (mg) / assigned daily dose (mg) Calculated for each cycle and overall for each patient Note: Daily dose here is determined by assigned or actual cycle length, not just the daily dose given in the dosing period
Components required for calculations above	**Definitions or Rule**
Total actual drug taken (mg)	Per patient, per cycle, equal to ((the number of tablets dispensed – number of tablets returned)*tablet strength) summed across tablet strength Per patient, the total drug taken per cycle summed over all cycles.
Prescribed exposure days	Days in the dosing interval – days omitted due to non-compliance Note: reasons due to non-compliance are any reasons for an omitted dose that are not due to adverse event (AE) (for example, patient decision or scheduling conflict)
Total expected (prescribed) drug (mg)	Per patient, per cycle: sum of (prescribed exposure days x daily prescribed dose) across different prescribed daily doses Daily prescribed dose is taken from 'Cycle 1 Day 1 Dose 1' and 'Study Treatment Changes' clinical (case) report forms (CRFs) Per patient, the total prescribed drug per cycle summed over all cycles
Total Assigned Drug (mg)	Per patient, per cycle: LY2157299: Sum of (expected days exposure in cycle*300) where expected days exposure in Cycle 1=13.5, expected days exposure in Cycle 2+ = 14 and expected days exposure in the last incomplete cycle = date of last dose in cycle – date of first dose of cycle +1 Per patient, the total assigned drug per cycle summed over all cycles Sorafenib: Sum of (expected days exposure in cycle*800) where expected days exposure in Cycle 1 is 27.5, expected days exposure in Cycle 2+ = 28 and expected days exposure in the last incomplete cycle = date of last dose in cycle – date of first dose of Cycle +1 Per patient, the total assigned drug per cycle summed over all cycles
Total days of actual exposure at each prescribed dose	Per patient, per cycle, per dose: Days of exposure = sum (date of last dose – date of first dose +1) taken from the chronology of dates from 'Cycle 1 Day 1 Dose 1', 'Study Treatment Changes' and 'Study Treatment Last Dose' CRFs The total days of actual exposure over all doses prescribed during a cycle should be: LY2157299: 13.5 for Cycle 1 and 14 for Cycle 2+ (unless planned omission or incomplete last cycle). Sorafenib: 27.5 for Cycle 1 and 28 for Cycle 2+ (unless planned omission or incomplete last cycle). Total days of actual exposure for a patient in the study is the sum of exposure days across all cycles

Compliance and Dose Intensity Definitions

Term	Definitions or Rule
Total days expected to be on study given number of cycles completed and length of last cycle on study treatment (excludes any dose delays)	Per patient, per cycle: 28 for all completed cycles and (date of study treatment discontinuation- date of first dose in last cycle+1) for the last cycle on study treatment Per patient: Days expected to be on study=(number of started cycles-1)*28 + (date of study treatment discontinuation- date of first dose in last cycle+1)
Total actual days on study (includes dose delays)	Per Patient, per cycle: Date of first dose in cycle (x+1) – date of first dose in cycle (x) for all cycles except the cycle started. Number of days on last cycle started = date of study treatment discontinuation – date of first dose in last cycle Per patient: Date of study treatment discontinuation – date of first dose +1 (should be equivalent to the sum of days on study across cycles)
Assigned daily dose	Per patient, per cycle: Total assigned drug/total expected days for each cycle Per patient: Total assigned drug across cycles/total days expected to be on study across cycles
Actual daily dose	Per patient, per cycle: Total actual drug taken/total actual days for each cycle Per patient: Total actual drug across cycles/total actual days on study across cycles Note: This is NOT the same as the sum of the assigned daily dose per patient per cycle/number of cycles.

Using the compliance and dose intensity derived for each patient as above, compliance and dose intensity will be summarised for LY2157299 and sorafenib by the following listing and table:

- Listing of oral dosing information including tablets distributed, returned, taken and prescribed at each cycle, dose adjustments, omissions and cycle delays, percent compliance per cycle and overall per patient.
- Summary of dose intensity per patient.

Further exposure summaries of LY2157299 and sorafenib include a summary of the number of patients completing each cycle and a summary of study drug administration including the number of patients with doses given as planned, with doses that were reduced, and with cycle delays.

6.12.2. Adverse Events

An **adverse event (AE)** is an event occurring after informed consent; or an event that is the same as a preexisting condition but has increased in severity/seriousness/relatedness after informed consent was signed; or a historical condition that recurs after the informed consent has been signed.

Preexisting conditions and AEs will be entered on the CRFs as follows. If a preexisting condition has not resolved at the time of study entry, and there are changes in severity, becomes serious without a change in severity, or the condition is considered related to study treatment or

procedures by the investigator, the event is classified as an AE and a new record with a new start date is entered in the AE CRF. If a condition that had already ended recurs after the informed consent has been signed, then the recurrence is classified as an AE and is entered with the new start date in the AE CRF. Any other events that occur after the informed consent is signed are entered in the AE CRF. If the AE has not resolved but there is a change in severity (or there is a change in seriousness not related to severity), then the date of the change is entered as the end date and a new AE record is generated. The start date of the new AE will be the date of the new status and will be equal to the end date of the previous status.

AEs will be coded using the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 or higher and MedDRA (MedDRA Version 16.0 or higher) and two hierarchies will be in SDTM. The MedDRA hierarchy will be created centrally by mapping the verbatim reported term to a MedDRA lower level term (LLT) and preferred term (PT) and, for the second hierarchy, the mapping will be from the investigator reported CTCAE term (except in the case "other-specify" within an SOC where the LLT will be obtained from the centrally mapped term, but will also be stored in a variable prefixed by CTC). All AE summaries will use the mappings to LLT, PT and SOC from the investigator reported CTCAE. Only variables prefixed by CTC in the AE or AE suppqual SDTM domains will be used in reporting.

A **treatment emergent AE (TEAE)** is any AE initially occurring after 1st dose; or if initially occurring pre-dose and ongoing at time of first dose (may be a pre-existing condition or AE) and severity of the reoccurrence is greater than the max severity pre-dose; then the reoccurrence is a TEAE. The time frame post-dose includes end of short term follow up period. The CTC LLT will be used to compare pre-dose and post-dose events in the TEAE algorithm.

1. Compare the post-dose LLT with LLT of preexisting conditions/AEs ongoing at first dose:
    a. If the post-dose LLT is not present as a pre-dose term, then the AE is a TEAE
    b. If the LLT is present as a pre-dose term AND the severity increases post-dose compared with the most severe pre-dose grade for the same LLT, then the event is a TEAE
2. Time frame post-dose includes end of short term follow up period – that is, 30 days post discontinuation of study treatment.

Treatment-emergent AEs excludes any AE which maps to a LLT recorded at baseline and has the same or lower severity as that at baseline, even if considered drug related or serious.

Treatment-related AEs are events considered as having at least a suspected relationship to the study drug as entered on the CRF.

If the severity grade or relationship to the study drug of an AE is missing, a worst-case scenario will be assumed (that is, Grade 4 or related for post-dose AEs, and Grade 1 or not related for pre-dose AEs).

Specifically, the following summary tables will be provided:

- An overview of AEs including the number and percentage of patients with ≥1 TEAE, ≥1 CTCAE Grade 3/4, ≥1 SAE, who discontinued study treatment due to AE, discontinued study treatment due to SAE, died due to AE on study treatment, and died due to AE within 30 days of discontinuation from study treatment. Additionally, the number of AEs related to study treatment in each of the previous categories will be given.
- The number and percentage of patients experiencing the following TEAEs by treatment group, SOC and PT:
    - TEAEs
        - Related and regardless of relatedness to study drug
    - TEAEs leading to discontinuation from study treatment
    - TEAEs leading to discontinuation from study treatment by serious criteria
        - Related and regardless of relatedness to study drug
    - SAEs
    - TEAEs by maximum reported CTCAE grade
        - Related and regardless of relatedness to study drug
    - TEAEs grouped by maximum CTCAE grade (Any grade, Grades 1/2, Grades 3/4/5, Grade 5)
        - Related and regardless of relatedness to study drug
- The number and percentage of patients experiencing the following TEAEs by treatment group and PT:
    - TEAEs leading to death (also see Section 6.12.4)
- The number and percentage of patients experiencing laboratory CTCAEs
    - Maximum derived CTCAE grade by cycle/visit
    - Shift from baseline to worst CTCAE grade post baseline by laboratory parameter

In the tabulations a patient with multiple adverse events within a SOC or PT is only counted once towards the total of this SOC or PT.

All AEs will be listed by treatment group, patient and onset date. Additionally, a separate listing will subset all SAEs. The definition of TEAE allows for the possibility of a treatment-related AE that is not classified as treatment emergent (for example, a treatment related AE that occurs after treatment has started that is the same severity as the same AE that occurred prior to treatment). Any AEs fitting this category will be listed.

6.12.3. Clinical Laboratory Evaluation

Table JBAS.6.6 describes the clinical laboratory tests to be performed and whether the test will be performed locally or centrally:

Table JBAS.6.6. Clinical Laboratory Tests

Hematology[a]
Hemoglobin
Erythrocyte count (RBC)
Leukocytes (WBC)
Neutrophils, segmented + bands
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets

Immunophenotype[b]

Urinalysis[a]
Specific gravity
pH
Protein
Glucose
Ketones
Blood
Leukocyte esterase

ECG chemistry[b]
Lipase
Thyroid stimulating hormone
Tri-iodothyronine
Thyroxine
Calcium[c]
Glucose, random (nonfasting)[c]
Albumin[c]
Phosphorus[c]
Sodium[c]
Potassium[c]
Magnesium[c]

Special chemistry[b]
Cystatin C
Troponin I
BNP
High-sensitivity C-reactive protein

Hepatitis B and C serology and panels[b]
Hepatitis B surface antigen
Hepatitis B surface antibody
Total hepatitis B core antibody
Hepatitis B e antigen
Hepatitis B e antibody
Hepatitis B virus DNA
Hepatitis C RNA

Clinical chemistry[b]
Serum concentrations of:
Total bilirubin
Direct bilirubin
Total protein
Alkaline phosphatase
LDH
Creatine kinase
Alanine aminotransaminase/serum glutamic pyruvic transaminase
Aspartate aminotransferase/ Serum glutamic oxaloacetic transaminase
Blood urea nitrogen
Creatinine
Uric acid
Calcium
Glucose, random (nonfasting)
Albumin
Cholesterol
Phosphorus
Sodium
Potassium
Magnesium

Serum markers [b]
AFP`
AFP L3
PIVKA II
E-cadherin

TGF-β+PF4[b]

Coagulation[b]
aPPT
PT
INR

Fibrotest[b]

Urine C-terminal telopeptides of Type 1 Collagen[b]

MAP[b]

Serum pregnancy test (females only)[a]

Clinical Laboratory Tests (Abbreviations)

Abbreviations: AFP = alpha-fetoprotein; aPTT = activated partial prothrombin time; BNP = brain natriuretic peptide; ECG = electrocardiogram; INR = international normalized ratio; LDH = lactate dehydrogenase; MAP = multi-analyte panel; PF4 = platelet factor 4; PIVKA II = prothrombin induced by vitamin K absence; PT = prothrombin time; RBC = red blood cell; TGF-β = transforming growth factor beta; WBC = white blood cell.

[a] Performed at local laboratory.

[b] Performed at central laboratory. Performed at a local laboratory if performed during the treatment extension period.

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

A listing of all hematology, chemistry (serum, special, ECG), urinalysis, Hepatitis B and C serology and panels, immunophenotype, serum markers, TGF-β +PF4, coagulation (aPPT/PT/INR), fibrotest, urine C-terminal telopeptides of Type 1 collagen, and multi-analyte panel (MAP) will be provided by treatment, patient, cycle and cycle day. Results will be presented using SI units (International System of Units), when available. Normal reference ranges and flags for out-of-range results will also be included. Relevant hematology and chemistry will be graded according to CTCAE v4.0 grading.

6.12.4. Deaths

Reasons for death will be summarized for all deaths, deaths occurring while on therapy, deaths occurring within 30 days of last dose of study drug, and for deaths on-therapy and within 30 days of last dose of study drug combined. Information regarding death will also be included in a data listing.

6.12.5. Hospitalizations and Blood Transfusions

Hospitalizations and blood transfusions will be collected during the study treatment period and during the 30-day post discontinuation follow-up period (Visit 801).

The number of subjects requiring hospitalization, the number of hospitalizations per subject, and duration of hospital stay for each event and for each subject will be summarized by treatment group using descriptive statistics. Any patients with a hospitalization admission and discharge date on the same day are counted as a half-day in the duration of hospitalization. End dates will be imputed as the data cutoff date for patients with hospitalization ongoing at the time of analysis.

A listing of all patients who were hospitalized will be provided. The listing will include the reason for hospitalization (that is, AE, protocol test, or other), MedDRA PT, start and end dates, and duration of hospitalization.

The number of prior, concomitant, and post-discontinuation blood transfusions and transfused units per subject will be summarized by the type of blood product transfused (that is, packed red blood cells, whole blood, platelets, fresh frozen plasma, or other).

Additionally, patients that received prior, concomitant, and post-discontinuation transfusions will be listed. The listing will include the date of transfusion, type of blood products received, number of units transfused, and MedDRA PT for each patient.

6.12.6. Vital Signs and Other Physical Findings

Vital signs will be listed by patient, cycle and cycle day (baseline, Day 1 of each cycle, Day 14 of Cycles 1 and 2 only, and Visit 801). This listing will include height (at baseline), weight, heart rate, blood pressure, and ECOG performance status.

6.12.7. Cardiac Assessments

Cardiac assessments include ECG, echocardiography, chest computed tomography (CT) scan and/or MRI, ECG chemistry (see Section 6.12.3 Clinical Laboratory Evaluation) and cardiac related adverse events (SOC="cardiac disorders"; see Section 6.12.2 Adverse Events).

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 safety 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.

A central reading will be performed for ECG, and CT and MRI images and will be used in the study report.

6.12.7.1. Electrocardiograms

Electrocardiograms (ECGs) will be performed during screening (baseline), Cycle 2, 3, 4, and every other cycle (Cycle 6, Cycle 8, etc).

ECG assessment of normality and clinical significance will be listed by treatment group. Myocardial information and quantitative results including PR, QRS, QTc (corrected by concurrent RR), QTcB (Bazett's correction), QTcF (Fridericia's correction) and RR intervals will provided in patient listings.
Changes in ECG parameters from baseline will be calculated and summarized at each visit.

6.12.7.2. Echocardiographs with Doppler

Echocardiography (ECHO) with Doppler will be assessed at screening, Cycle 2, 3, 4, and every other cycle (Cycle 6, Cycle 8, etc), Visit 801 and long term follow up as described above.

Echocardiography measurement values and changes from baseline will be listed for the following quantitative data: LV internal dimension, LA volume, LA dimension, LV ejection fraction, LV mass, PA systolic pressure, pulmonary flow velocity acceleration time, mitral deceleration time, mitral E/A ratio, and E/Em. Results will be listed by treatment, patient, cycle/visit, and parameter.

Echocardiography assessments with valvular regurgitation (aortic, pulmonary, mitral, and tricuspid regurgitation) will be listed by treatment, patient, cycle/visit, and study day.

Additionally, the frequency of maximum shift from baseline will be summarized by parameter and treatment.

RA dilation, RV dilation, left ventricular wall motion, and pericardial effusion will be listed by treatment, patient, cycle/visit, and study day. Additionally, the frequency of maximum shift from baseline will be summarized by parameter and treatment.

Graphical representation of LVEF may be provided if necessary.

6.12.7.3. Chest Computed Tomography Scans

Chest computed tomography (CT) scan with contrast of thorax and abdomen for cardiac assessment will be assessed at screening and every 6 months throughout the study and at Visit 801. Alternatively, chest and/or abdomen MRI are allowed.

Chest CT scan with contrast of thorax and abdomen for tumor assessment will be assessed at screening and every 6 weeks starting Cycle 2 Day 14 until radiological disease progression. Alternatively, chest and/or abdomen MRI are allowed.

Results from the CT scan for cardiac assessment and for tumor assessment will be listed separately by treatment, patient and cycle/visit.

6.12.8. Other Data

CT lot numbers of LY2157299 will be listed by treatment, patient and cycle.

6.12.9. Protocol Violations

Significant protocol violations that potentially compromise the data integrity and patients' safety are listed by treatment group for all randomized patients.

Appendix 1 lists the categories of significant protocol violations, the detailed description of each violation within the category, and the method to identify each violation. Further details of study monitoring are in the Study Specific Monitoring Requirements (SSMR) document.

All data collected on the CRF will be checked programmatically for violations. Actual details specifying the programming methods will be given in the ADaM and table, figure, listing (TFL) specifications. Protocol violations that are documented in the monitoring database will be exported to an Excel file for import by statistics. Patients with significant violations may be excluded from the per-protocol population.

6.13. Interim Analyses and Data Monitoring

Three interim analyses are planned. Interim analyses will occur after approximately 10 patients have completed Cycle 1 in the LY2157299 plus sorafenib arm; after approximately 32 patients are randomized and have completed either 3 cycles of treatment, discontinued from study drug, or died; and after approximately 70 deaths have occurred in 3 arms.

Results will be reviewed by an internal assessment committee consisting of the Lilly Medical Director, a Lilly CRP not in contact with study sites, a Lilly statistician, and a PK scientist, if needed. The assessment committee members will review unblinded safety and/or efficacy data at each interim analysis to determine whether there are sufficient safety or futility concerns to

justify the termination of a study treatment arm. Results of the interim analyses will not be communicated to the study sites, unless the interim analyses show evidence of harm.

6.13.1. Interim Analysis #1

The first interim assessment is planned when approximately 10 patients have completed Cycle 1 in the LY2157299 plus sorafenib arm (approximately 3 months from when the first patient is randomly assigned to a treatment arm). It aims to evaluate the PK and safety profiles in the combination arm.

The plan is to continue enrolling patients during the interim assessment unless ongoing safety reviews have raised safety concerns.

6.13.2. Interim Analysis #2

The second interim assessment is planned when approximately 32 patients are randomized and have completed either 3 cycles of treatment, discontinued from study drug, or died (approximately 6 months from when the first patient is randomly assigned to a treatment arm).

The second interim analysis will aim to evaluate that patients treated with LY2157299 monotherapy are not at risk of receiving a treatment that is inferior to sorafenib. Bayesian OS analysis will be carried out at this interim analysis. The LY2157299 monotherapy may be considered futile if the posterior probability of seeing HR <0.667 is <10%. Table JBAS.6.7 summarizes the likelihood of futility under different HRs. FACTS (version 3.2) was used for simulations.

Table JBAS.6.7. Simulation Results for Interim Analysis #2

n	Allocation	Control Rate Prior	Timing of Analysis	HR	Posterior Probability (HR <0.667) <10%
32	1:2:1	Strong prior for interim analysis #2	First patient visit+7.1 months	1	19%
				1.5	43%
				2	65%
32	1:2:1	Weak prior for interim analysis #2	First patient visit +7.1 months	1	21%
				1.5	40%
				2	61%

Abbreviation: HR = hazard ratio.

6.13.3. Interim Analysis #3

The third interim assessment will be conducted for the purposes of detecting early efficacy signals as well as further evaluating safety observations. This interim analysis will be carried out after approximately 70 deaths have occurred in 3 arms and is projected to take place approximately 17 months after the first patient's visit. Bayesian OS analysis will be carried out at this interim analysis. No formal stopping rules for efficacy will be applied to the interim analyses so that no alpha adjustment will be made. Table JBAS.6.8 summarizes simulation results for type I errors and statistical powers using FACTS (version 3.2).

Table JBAS.6.8. Simulation Results for Interim Analysis 3

N (deaths)	Control Rate Prior	Timing of Analysis	Type I Error	Posterior Probability (HR <1) >0.84
120 (70)	Strong prior for interim analysis #3	first patient visit +20.4 months	14%	74%
120 (70)	Weak prior for interim analysis #3	first patient visit +20.4 months	15%	65%

Abbreviation: HR = hazard ratio.

6.14. Planned Exploratory Analyses

Exploratory analyses/data mining will be carried out on imaging data, fibrotest data, gene-expression data, MAP data, blood biomarkers data and tumor-tissue data as appropriate, investigating links between these data and clinical and PD efficacy endpoints. In addition, analyses between serological hepatitis status, dose adjustment and clinical outcome will be explored as appropriate. Definition of serological hepatitis status using Hepatitis B and C serology and panels will be defined in the Analysis Data Model (ADaM) and/or Table Figure Listing (TFL) programming specifications. Using serological hepatitis status in the analysis is in addition to the primary analyses using disease etiology which includes Hepatitis B and Hepatitis C. The data will be investigated if there is a major difference between frequencies of hepatitis status defined by disease etiology and serological assessment.

6.15. Annual Report Analyses

The Annual Report is replaced by the Development Safety Update Report (DSUR). The following reports will be produced for the DSUR:

- Exposure
- Disposition
- Demographics
- Listing of subjects who died during the DSUR period
- Discontinuations due to adverse event during the DSUR Period.

For further details on these reports, see the DSUR collaboration site: http://lillynetcollaboration.global.lilly.com/sites/GMRS_GPS/Surv/dsur/default.aspx?PageView=Shared

6.16. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA Preferred Term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. References

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Filbiberti A, Flechtner H, Fleishman SB, de Haes JC, Klee D, Osoba D, Razavi B, Rofe S, Schraub K, Sneeuw M, Sullivan M, Takeda F. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in Oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.

Blazeby JM, Currie E, Zee BC, Chie WC, Poon RT, Garden OJ, EORTC Quality of Life Group. Development of a questionnaire module to supplement the EORTC QLQ-C30 to assess quality of life in patients with hepatocellular carcinoma, the EORTC QLQ-HCC18. *Eur J Cancer.* 2004;40(16):2439-2444.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics. 1982;*38:29–41.

Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26:404–413.

Dmitrienko A, Smith B. Repeated-measures models in the analysis of QT interval. *Pharmaceutical Statistics* 2003; 2:175-190.

Han B, Enas NH, McEntegart D. Randomization by minimization for unbalanced treatment allocation. *Stat Med*. 2009;28(27):3329-3346.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc.* 1958;53:457-481.

Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31(1):103-115.

8. Appendices

Appendix 1. List of Protocol Violations for H9H-MC-JBAS

Table 1. Description of Significant Protocol Violations

Category of Significant Protocol Violation/Violation Details	Methods of Identification
Violation of key inclusion/exclusion criteria (Protocol Section 7.1 and 7.2)	
General	Identified both by CRA during monitoring and programmatically, if "Failure to Meet Randomization Criteria" is marked on CRF but patient moves on to Visit 1.
Criteria [1], [8] – [28]	Identified solely by CRA during monitoring
Criteria [2]	Identified both by CRA during monitoring and programmatically, if stage is not Child-Pugh Stage A in CLIP CRF.
Criteria [3]	Identified both by CRA during monitoring and programmatically, if baseline tumor measurements in CRF data indicate tumor is measureable based on RECIST v1.1.
Criteria [4]	Identified both by CRA during monitoring and programmatically, if CRF data indicate the Age <= 18 yrs at Visit 0.
Criteria [5]	Identified both by CRA during monitoring and programmatically, if the date of informed consent is missing or it is after the Visit 1 date.
Criteria [6]	Identified both by CRA during monitoring and programmatically. Potential violations are identified programmatically, if central laboratory data do not meet required levels at Visit 1.
Criteria [7]	Identified programmatically, if CRF data indicate ECOG scale >1 at Cycle 1 (Visit 1)
Significant patient assessment or management issues	
Incorrect treatment assignment based on AFP and portal vein thrombosis levels	Identified both by CRA during monitoring and programmatically, if dynamic randomization schedule is available for cross-checking.
Study drug not omitted in the case of indicated AEs which are considered at least possibly related to study treatment	Identified both by CRA during monitoring and programmatically. Patients with the following central laboratory data results and associated treatment-related AEs will be listed for further review: ANC <0.5 10^9/L (duration of longer than 7 days to be checked by CRA) ANC <1.0 10^9/L (temperature to be checked by CRA: those 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) Platelet count <25 10^9/L. CTCAE Grade 3 or 4 nonhematologic toxicity. CRA will check that study drug is omitted from time of AE onset until adequate resolution (in the case of hematological toxicity, the definition of resolution is according to the investigator's opinion).
LY 2157299 dose reductions not occurring as specified	Identified both by CRA during monitoring and programmatically. dose reduction did not occur after qualifying AE >1 dose reduction (without reescalation) during the course of the study or, if reescalated, >1 dose reduction after reescalation during the course

	of the study >1 reescalation occurs during the course of the study Patient not withdrawn from LY2157299 if dosing is delayed for >2 weeks for treatment-related AEs
Lack of subject compliance with treatment	Identified both by CRA during monitoring and programmatically. List any subjects with compliance per cycle that is <80% or >120%.
Prohibited concomitant therapy	Identified both by CRA during monitoring and programmatically by verifying no prohibited medications are in CRF data. other anti-cancer therapy (chemotherapy, target therapy, radiotherapy, except palliative radiation to non-target lesions); immunotherapy; hormonal cancer therapy; experimental/investigational medication; Rapamycin analogues; Increased immunosuppressive therapy (patients on maintenance immunosuppressive therapy after liver transplant are eligible); 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, and aromatase inhibitor) may have that treatment continued while they are enrolled in this study.
Failure to perform PK collections	Identified both by CRA during monitoring and programmatically. Note: only collections "not done" are considered significant protocol violations.
Failure to perform safety assessments	Failure to perform safety procedures or missing safety measurements per requirements in Study Schedule (Attachment 1 in Protocol). Hematology/chemistry; CT and MRI ECG ECHO and Doppler Identified both by CRA during monitoring and programmatically. Note: only collections "not done" are considered significant protocol violations.
Failure to perform efficacy assessments	Failure to perform efficacy procedures or missing efficacy measurements. Radiological Tumor Assessments per RECIST and mRECIST. Palpable/visible (as applicable). Identified both by CRA during monitoring and programmatically. Note: only collections "not done" are considered significant protocol violations.
Violation of discontinuation criteria	
Discontinuation criteria met but patient not removed from study (see Protocol Section 7.3.1)	Identified both by CRA during monitoring and programmatically: Discontinuation CRF data indicate criteria was met Lab data or the CRF AE page indicate that the subject was pregnant during the treatment. If echocardiography with Doppler data indicate moderate or severe heart valve toxicities are observed and patient is not removed from study.
Verify that the investigator has signed the CRF for all subjects who have screen failed, early discontinued, or completed the trial.	Identified both by CRA during monitoring and programmatically, if subject discontinued and Casebook Signature CRF is not completed.

Other	
Patient received drug that was declared "not Fit for Use"	Identified solely by CRA during monitoring.
Inadvertent un-blinding	Identified solely by CRA during monitoring.
Drug dispensing errors	Identified solely by CRA during monitoring.
Maintenance and calibration issues with critical equipment	Identified solely by CRA during monitoring. Verify maintenance and calibration records are current during the study for the following critical equipment: ECHO with Doppler Imaging Machines (CT/MRI) ECG If Applicable at site: DCE-MRI and/or DW-MRI Equipment needed to extract optional biopsy tissue
Other protocol violations that result in study discontinuation	As recorded on the CRF discontinuations page.

Abbreviations: AE = adverse event; CRA = clinical research associate; CRF = case report form; CT = computed or computerized tomography; DCE = Dynamic Contrast Enhanced; DW = diffusion weighted; ECG = electrocardiogram; ECHO = echocardiogram; MRI = magnetic resonance imaging.

Leo Document ID = b8cb3cf7-15b0-40a1-8f2d-8cd00cf2a27b

Approver: PPD
Approval Date & Time: 26-Jul-2017 01:50:30 GMT
Signature meaning: Approved