The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Linifanib versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma: Results of a Randomized Phase III Trial.

Cainap, et al

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Supplemental Tables and Figures

S1. Summary of Drug Exposure

	Sorafenib N=521	Linifanib N=514
Duration of Study Drug, days		
Mean	127.8	127.2
Median	84	87
Range	3 - 729	2 - 775
Duration [Interval Days], n (%)		
>0 – 21	54 (10.4)	77 (15.1)
>21 – 42	93 (17.9)	62 (12.2)
>42 – 63	83 (16.0)	55 (10.8)
>63 – 84	37 (7.1)	47 (9.2)
>84 – 105	42 (8.1)	48 (9.4)
>105	210 (40.5)	221 (43.3)
Average Daily Dose, mg		
Mean	667.1	13.7
Median	765.9	13.8
Range	200 - 800	3.2 – 70
Dose Intensity, %		
Mean	83.4	78.2
Median	95.7	78.8
Range	25 - 100	18.6 - 400

S2. Percent Change in Alpha-fetoprotein (AFP) at Week 6

	N	Mean	Median	Q1 – Q3	p-value
Linifanib, N = 514	359	-42.9	-35.0	-66.7 – 3.0	<0.001
Sorafenib, N = 521	379	-8.0	1.7	-28.9 – 62.7	

1.0 Title Page

CLINICAL STUDY PROTOCOL M10-963

An Open-label, Randomized Phase 3 Study of the Efficacy and Tolerability of Linifanib (ABT-869) versus Sorafenib in Subjects with Advanced Hepatocellular Carcinoma (HCC)

Incorporating Amendment 1 (Japan Only), Amendment 2 (Global), Amendment 3 (China Only), Amendment 4 (Global) and Amendment 5 (Japan Only)

Abbott Investigational Product:	Linifanib (ABT-869)	
Date:	28 March 2011	
Development Phase:	3	
Study Design:	An Open-label, Randomized Phase 3 Study of Efficacy and Tolerability of Linifanib (ABT-869) in Advanced Hepatocellular Carcinoma (HCC)	
EudraCT Number:	2009-013435-38	
Investigators:	Multicenter Trial: Investigator information is on file at Abbott	
Sponsor:	Abbott Laboratories (Abbott), Abbott GmbH & Co. KG, Abbott Japan Co., Ltd. Abbott Laboratories S.A.	
Sponsor/Emergency Contact:	Justin L. Ricker, MD, PhD Medical Director Abbott Laboratories Dept. R48K, Bldg. AP30-3 200 Abbott Park Rd. Abbott Park, IL 60064-6146	Phone: (847) 937-2345 Cell: (847) 224-0556 Fax: (847) 937-8460

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

4.0 Study Objective

The primary objective of this study is to evaluate the overall survival of oral linifanib given as monotherapy daily compared to sorafenib given twice daily as standard of care in subjects with advanced or metastatic HCC. The secondary objectives of this study are to evaluate time to progression and objective response rate in those subjects treated with linifanib compared with sorafenib. The tertiary objectives will include comparison of progression free survival and of the quality of life (QoL) between linifanib and sorafenib treatments.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, randomized, open-label, multinational, multicenter study to evaluate the efficacy and tolerability of linifanib compared to sorafenib in subjects with advanced or metastatic HCC who have not received prior systemic therapy.

Subjects will be randomized in a 1:1 ratio to 1 of the 2 treatment groups (linifanib or sorafenib). Approximately 900 to 1,100 subjects will be enrolled at approximately 200 sites. Two interim analyses are planned (Section 8.1.10).

Linifanib is an oral tablet administered at 17.5 mg QD. Subjects will be trained to self administer linifanib as described in Section 5.5.1.2.

Sorafenib is an oral tablet administered at 400 mg BID. Subjects will be trained to self administer sorafenib as described in Section 5.5.1.1.

The Screening procedures and baseline radiographic tumor assessments should be performed within 21 days prior to the first dose of study drug (Study Day 1). If the Screening Visit is performed greater than 7 days prior to Study Day 1, the physical exam, laboratory tests, and a pregnancy test (for female subjects of childbearing potential) must be repeated on Study Day 1 prior to dosing. Vital signs and performance status assessment will be performed on Study Day 1 for all subjects prior to dosing.

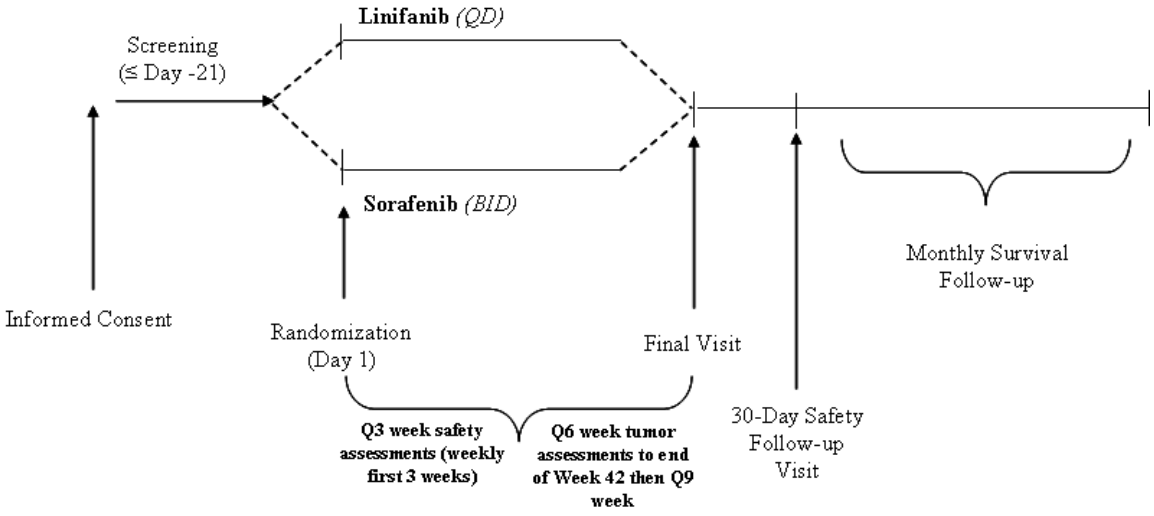
Study visits will be conducted on Day 1 of the first 3 weeks (i.e., Study Day 1, Day 1 of Week 2, Day 1 of Week 3) and then on Day 1 of every 3 weeks thereafter (starting with Week 4). Subjects will continue dosing with linifanib or sorafenib until they meet the discontinuation criteria discussed in Section 5.4.1. When an investigator has determined that a subject should discontinue the study, a Final Visit will be conducted.

All subjects will have one Follow-up Visit approximately 30 days after the last dose of linifanib or sorafenib. This Follow-up Visit does not need to be conducted if the Final Visit is $\geq$ 30 days after the last dose of linifanib or sorafenib.

Post-study assessments, including survival (e.g., the date and cause of death), post-treatment and health resource utilization information will be collected via Interactive Voice or Web Response System (IVRS/IWRS) at monthly intervals (or as requested by sponsor to support data analysis) after the last study visit until the endpoint of death or until the subject has become lost to follow-up or until study termination by Abbott.

A schematic of the study design is shown in Figure 1.

Figure 1. Study Schematic



5.2 Selection of Study Population

Subjects will be adults with advanced or metastatic HCC who meet all of the inclusion criteria and none of the exclusion criteria within 21 days prior to the first day of study treatment.

5.2.1 Inclusion Criteria

1. Subject must be an adult ≥ 18 years of age.

2. Subject must be diagnosed with unresectable or metastatic HCC defined by:

   - Histologic or cytologic diagnosis OR
   - European Association for the Study of Liver Criteria[13] (restricted to cirrhotic subjects) which includes a focal lesion > 2 cm with arterial hypervascularization and either:
     - Radiological criteria: two coincident imaging techniques (Four techniques considered: ultrasound, spiral computed tomography (CT), magnetic resonance imaging (MRI) and angiography) OR
     - Combined criteria: one imaging technique associated with AFP (alpha fetoprotein) > 400 ng/mL

3. Subjects must have a measurable lesion by RECIST (version 1.1) on CT scan in at least one site which has not received prior radiotherapy.

4. Subjects must show signs of progression (i.e., new lesion per RECIST version 1.1) if prior liver-directed therapy was received.

5. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 1.

6. Subject must have the following laboratory values:

   - Total Bilirubin $\leq$ 3.0 mg/dL or equivalent
   - AST/ALT $\leq 5 \times$ ULN
   - PTT $\leq 1.5 \times$ ULN and INR < 1.5
   - ANC $\geq 1.0 \times 10^9$/L
   - Platelet count $\geq 50 \times 10^9$/L if splenomegaly; if splenomegaly is not present, platelet count $\geq 75 \times 10^9$/L. Patients are considered to have splenomegaly if diagnosed by physical exam or reported on radiographic imaging.
   - Serum Creatinine $\leq 1.5 \times$ ULN
   - Serum Albumin $\geq$ 2.8 g/dL

- PT ≤ 6 seconds prolonged

7. Women of childbearing potential and men must agree to use adequate contraception (one of the following listed below) prior to study entry, for the duration of study participation and for 90 days following completion of therapy. Women of childbearing potential must have a negative urine pregnancy test within 7 days prior to initiation of treatment and/or post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.

   - Total abstinence from sexual intercourse (for minimum of one complete menstrual cycle prior to study drug administration),
   - Vasectomized male subjects or vasectomized partner of female subjects,
   - Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration,
   - Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream),
   - Intra-Uterine Device,
   - Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms for the duration of the study and for 90 days following completion of therapy.

8. Subject is capable of understanding and complying with parameters as outlined in the protocol and able to sign informed consent, approved by an Independent Ethic Committee (IEC)/Institutional Review Board (IRB) prior to the initiation of any screening or study-specific procedures, and in the opinion of the Study Investigator with agreement by the subject, currently no other treatment options exist that will provide benefit to the subject and/or the subject is willing to receive (e.g., transcatheter arterial chemoembolization).

Rationale for Inclusion Criteria

(1-5) To select the appropriate subject population with sufficient disease severity for evaluation.

(6) For the safety of the subjects.

(7) The impact of linifanib and sorafenib on pregnancies is unknown.

(8) In accordance with harmonized Good Clinical Practice.

5.2.2 Exclusion Criteria

1. Subject has received prior systemic (administered intravenously or orally rather than locoregionally) treatment for HCC.

2. Subject has Child-Pugh grade Class B or C hepatic impairment.

3. Subject has received prior local therapy (including liver-directed therapy) within 4 weeks prior to study drug administration or subject has received radionuclide treatment (i.e., ^{90}Yttrium intra arterial treatment) within the last 6 months (or 5 half-lives, whichever is shorter) prior to study drug administration. Local therapies include but are not limited to: surgery, radiation therapy, hepatic arterial embolization, hepatic intra-arterial chemotherapy, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation. In addition, subject has not recovered to $\leq$ Grade 1 clinically significant adverse effects/toxicities of previous therapy.

4. Subject has untreated brain or meningeal metastases. CT scans are not required to rule out brain or meningeal metastases unless there is a clinical suspicion of central nervous system disease. Subjects with treated brain metastases that are radiographically or clinically stable (for at least 4 weeks after therapy) and have no evidence of cavitation or hemorrhage in the brain lesion, are eligible provided that

they are asymptomatic and do not require corticosteroids (must have discontinued steroids at least 1 week prior to Study Day 1).

5. Subject has previous or concurrent cancer that is distinct in primary site or histology from HCC except cervical carcinoma in situ, non-melanoma carcinoma of the skin or in situ carcinoma of the bladder. Any cancer curatively treated greater than 3 years prior to entry is permitted.

6. Subject has proteinuria defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade > 1 at baseline as measured by a urine dipstick (2+ or greater) and confirmed by a 24 hour urine collection (> 1 g/24 hrs). Subjects may be re-screened if proteinuria is shown to be controlled with or without intervention.

7. Subject currently exhibits symptomatic or persistent, uncontrolled hypertension defined as diastolic blood pressure > 90 mmHg or systolic blood pressure > 140 mmHg. Subjects may be re-screened if blood pressure is shown to be controlled with or without intervention.

8. Subject has a documented Left Ventricular Ejection Fraction < 50%.

9. Subject is receiving therapeutic anticoagulation therapy. Low dose, non-therapeutic anticoagulation (e.g., low dose warfarin) for catheter prophylaxis only will be permitted.

10. Subject is receiving anti-retroviral therapy for Human Immunodeficiency Virus (HIV). Prophylactic antiviral therapy to prevent Hepatitis B virus (HBV) reactivation or cytokine therapy (e.g. interferon) for Hepatitis C virus infection is allowed.

11. Female subjects who are pregnant or breast feeding.

12. Presence of > grade 2 encephalopathy by NCI CTCAE criteria.

13. Presence of moderate ascites. Mild ascites controlled with diuretics is allowed.

14. Clinically significant uncontrolled condition(s) including but not limited to:

- Active uncontrolled infection
- Class III or IV heart failure as defined by the New York Heart Association functional classification system
- Unstable angina pectoris or cardiac arrhythmia
- Myocardial infarction within last 6 months
- History of a liver transplant
- History of adrenal insufficiency
- History of cerebral vascular accident within last 6 months
- Active ulcerative colitis, Crohn's disease, celiac disease or any other conditions that interfere with absorption
- History of autoimmune disease with kidney involvement
- History of overt bleeding (> 30 mL bleeding/episode) within 3 months of study drug administration
- Psychiatric illness/social situation that would limit compliance with study requirements
- Any medical condition, which in the opinion of the study investigator places the subject at an unacceptably high risk for toxicities.

Rationale for Exclusion Criteria

(1, 2, 5, 12-13) To select the appropriate subject population with sufficient disease severity for evaluation.

(3, 4, 6-10, 14) For the safety of the subjects.

(11) The impact of linifanib and sorafenib on pregnancies is unknown.

5.3 Efficacy Pharmacokinetic, Pharmacodynamic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

A schedule of study activities is presented in Table 2. A schedule of pharmacodynamics (PD), pharmacokinetics (PK), and pharmacogenetics (PG) activities is presented in Table 3.

Table 2. Study Activities

Activity	Screening[a]	Day 1 of Week 1 (Study Day 1)	Day 4 of Week 1 and Week 2[k]	Day 1 of Weeks 2 and 3	Day 1 of Every 3 Weeks (Beginning with Week 4)	End of Every 6 Weeks	Day 1 of Every 12 Weeks	Final Visit	Follow-up Visit[i]	Post-treatment
Informed Consent	X									
Medical History	X									
Physical Exam[j]	X[b]	X[c]	X	X	X			X	X	
Vital Signs	X	X	X	X	X			X	X	
Performance Status (ECOG)	X	X		X	X			X	X	
12-lead ECG	X						X	X[e]		
MUGA or Echocardiogram	X						X	X[e]		
Pregnancy Test (if applicable)	X	X[c]								
Hepatitis B Surface Antigen (HBsAg)/Hepatitis C virus antibody (HCV Ab) Tests	X									
Hematology[d]	X	X[c]		X	X			X	X	
Chemistry[d]	X	X[c]	X[l]	X	X			X	X	
Urinalysis[d]	X	X[c]		X	X			X	X	
Tumor Assessments	X					Xf		Xe		

Table 2. Study Activities (Continued)

Activity	Screening[a]	Day 1 of Week 1 (Study Day 1)	Day 4 of Week 1 and Week 2[k]	Day 1 of Weeks 2 and 3	Day 1 of Every 3 Weeks (Beginning with Week 4)	End of Every 6 Weeks	Day 1 of Every 12 Weeks	Final Visit	Follow-up Visit[i]	Post-treatment
Quality of Life Surveys	X				X[g]			X	X	
Health Resource Utilization Questionnaire	X				X			X	X	
Monitor Adverse Events		X	X	X	X			X	X	
Monitor Study Drug Administration Compliance			X	X	X			X		
Dispense Study Drug		X			X					
Post-treatment Assessments										X[h]

a. The Screening Visit should be performed within 21 days of Study Day 1.

b. Height will be measured at Screening only.

c. Physical exam, labs and pregnancy test not required if performed within 7 days prior to Study Day 1.

d. Refer to Table 4 for detailed list of tests to be performed and frequency.

e. To be performed at Final Visit only if not performed within the last 4 weeks.

f. Tumor assessments will be conducted every 9 weeks starting after the end of Week 42 assessment.

g. QoL to be collected every 3 weeks (i.e., Day 1 of Week 4, Day 1 of Week 7, Day 1 of Week 10, etc.).

h. Post-treatment assessments will be collected monthly unless requested by Sponsor more frequently to support data analysis.

Table 2. Study Activities (Continued)

i. Follow-up Visit does not need to be performed for subjects who have had a Final Visit conducted ≥ 30 days after the last dose of study drug.

j. Including encephalopathy/hepatic encephalopathy. A tool for the clinical assessment of hepatic encephalopathy is the TRAIL test.[26,27]

k. For subjects in Japan only.

l. Only liver function tests (total Bilirubin, SGPT/AST, SGOT/AST) will be assessed.

Table 3. Pharmacokinetic, Pharmacodynamic, and Pharmacogenetic Study Activities

Activity	Study Day 1	Day 1 of Week 2	Day 1 of Week 3	Day 1 of Weeks 7, 13 and 25	Day 1 of Weeks 37 and 52	Every 6 Weeks	Final Visit
Pharmacokinetic[a,b,e]		X	X	X	X		
Pharmacogenetic[a,c]	X						
Plasma Markers[a]	X	X	X			X[d]	X
Archived Tissue[c]	X						

a. All samples should be drawn in conjunction with clinical lab blood draws.

b. PK samples will be drawn only for those subjects randomized to the linifanib treatment arm.

c. Optional collection.

d. Day 1 of Week 7, Day 1 of Week 13, Day 1 of Week 19, etc.

e. Every effort should be made to collect a PK sample at the onset of an encephalopathy/ hepatic encephalopathy event.

5.3.1.1 Study Procedures

The study procedures outlined in Table 2 are discussed in detail in this section, with the exception of the collection of blood samples for pharmacodynamic, pharmacogenetic and pharmacokinetic analysis (discussed in Section 5.3.1.2, Section 5.3.1.3 and Section 5.3.2.1, respectively), the monitoring of treatment compliance (discussed in Section 5.5.7) and the collection of adverse event information (discussed in Section 6.0). All study data will be recorded on electronic case report forms (eCRFs) with the exception of the QoL questionnaires, health resource utilization questionnaires, PK, PD, and PG collections and pregnancy reporting forms, which will be recorded on paper CRFs.

Procedures performed at Screening will serve as baseline, unless repeated on Study Day 1 prior to dosing; in which case, the latter will serve as baseline. Subsequent study procedures should be performed within 4 days surrounding the scheduled study visit date.

For subjects in Japan only, study procedures should be performed within 1 day surrounding (up to 1 day before or 1 day after) the scheduled visit date for the Week 1 Day 4, Week 2 Day 1, Week 2 Day 4 and Week 3 Day 1 study visits. Subsequent study procedures should be performed within 4 days surrounding the scheduled study visit date.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative in order to participate in this study. The IRB/IEC approved informed consent must be signed and dated by each subject prior to undergoing any study procedures or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent will also be required for the PG, archived tissue, and ECG cohort portions of the study. Refer to Section 9.3 for details on obtaining and documenting informed consents.

Medical History

The following will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical condition.
- History of tobacco and alcohol use.
- History of cirrhosis and etiology (hemochromatosis versus alcoholic cirrhosis versus other).
- History of chronic hepatitis. Specify viral hepatitis (hepatitis B, C, other).
- Specify if disease is confined to liver or metastatic and if metastatic, to which organs.
- Presence and severity of any symptoms/conditions associated with HCC.
- Detailed HCC oncology history including:
    - Pathology, if available
    - Date of cancer diagnosis
    - Child-Pugh Category at enrollment
    - Any surgical procedures
    - Prior treatments administered (including dates and type of modality)
        - Hepatic arterial embolization
        - Hepatic intra-arterial chemotherapy
        - Chemoembolization
        - Radiofrequency ablation
        - Cryoablation
        - Percutaneous ethanol injection
        - Other treatments
- Other oncology history including prior anthracycline (total received), if known.

On Study Day 1, any changes observed from the Screening Visit will be recorded in the subject's medical history. At each subsequent visit, the subject's medical history will be reviewed and any clinically significant changes from baseline will be recorded in the source documents and on the adverse event eCRF.

All medication (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing until 30 days following the last dose of study drug.

HBsAg and HCV Ab Test

All subjects will have HBsAg and HCV Ab tests performed at Screening by the central laboratory. The results of the HBsAg test, not the information collected from medical history, must be used to stratify the subject in IVRS/IWRS. If a subject has concurrent HBV and HCV infection, the subject will be included in the HBV group.

Physical Examination

A complete physical examination (PE), including body weight, will be performed at Screening. A symptom-directed PE, including weight and assessment for encephalopathy/ hepatic encephalopathy will be performed at all other visits unless indicated otherwise. A tool that may be used for the clinical assessment of hepatic encephalopathy is the TRAIL test.[26,27] If it is determined clinically that a subject has encephalopathy/ hepatic encephalopathy, it should be recorded as an adverse event.

Height will be measured at Screening only. If the Screening PE is performed within 7 days of Study Day 1, PE is not required at Study Day 1, unless clinically indicated. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events.

Vital Signs

Vital sign determinations of sitting blood pressure, heart rate and body temperature will be measured at all visits. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed for all subjects at Screening and on Day 1 of every 12 weeks, and at the Final Visit if not conducted within the last 4 weeks. A qualified physician will determine if any findings outside normal physiological variation are clinically significant (in consultation with a cardiologist if necessary), document this on the ECG report and then sign and date the ECG report. The Screening ECG will be used to document baseline status of the subject so that safety comparisons can be made.

In addition, at approximately 1 to 4 study sites, triplicate ECGs (defined as first ECG after 5 minutes supine, second ECG approximately 60 seconds after the first ECG and third ECG approximately 60 seconds after the second ECG) will be obtained for a cohort of 30 evaluable subjects (who consent) randomized to receive linifanib. The details of the ECG cohort are provided in Appendix I.

ECOG Performance Status

The ECOG performance status will be assessed at all visits as follows unless indicated otherwise per Table 2.[17] A conversion for Karnofsky and ECOG scores is provided in Appendix E.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, 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.

Pregnancy Test

For female subjects of childbearing potential, a urine pregnancy test will be performed at Screening. If the screening pregnancy test is within 7 days of Study Day 1, a pregnancy test is not required at Study Day 1, unless clinically indicated. The test may be repeated at the discretion of the Investigator at any time during the study. A lactating or pregnant female will not be eligible for participation in this study.

Female subjects considered not of childbearing potential must be documented as being surgically sterile or post-menopausal for at least 1 year.

Clinical Laboratory Tests

All subjects will have the laboratory analyses performed as outlined in Table 4. All laboratory samples, except those performed on Day 4 of Weeks 1 and 2 for Japan subjects only, will be assessed using a certified central laboratory and these data will be used for all data analysis. The central laboratory for this study, ICON Central Laboratories (ICON) will provide instructions regarding the collection, processing and shipping of samples. All laboratory samples should be shipped to the central laboratory.

Samples collected at Day 4 of Weeks 1 and 2 for Japan subjects only will be assessed using a certified local reference laboratory and the results captured in the eCRF. The appropriate certifications will be collected for the local laboratory.

A certified local reference laboratory may perform hematology and chemistry tests for immediate subject management; however, split or concurrent samples should be drawn and sent to the central laboratory for analysis. The appropriate certifications will be collected for both the central and local laboratories as needed.

Samples for chemistry, hematology and urinalysis will be collected at all visits. If Screening labs are performed within 7 days of Study Day 1, clinical laboratory tests (hematology, chemistry and urinalysis) do not need to be repeated on Study Day 1 unless clinically indicated. For all subjects other than those in Japan, after Study Day 1, clinical laboratory tests should be performed within 4 days surrounding the scheduled study visit date. For a detailed list of tests and frequencies, refer to Table 4.

For subjects in Japan only, samples for chemistry (liver function tests only; total bilirubin, SGPT/ALT, SGOT/AST) will be collected at Day 4 of Weeks 1 and 2 and assessed locally. For subjects in Japan only, clinical laboratory tests should be performed within 1 day surrounding (up to 1 day before or 1 day after) the scheduled visit date for the Week 1 Day 4, Week 2 Day 1, Week 2 Day 4 and Day 1 Week 3 study visits. Beginning with Day 1 Week 4, clinical laboratory tests should be performed within 4 days surrounding the scheduled study visit date.

As a conservative measure to monitor for potential cardiac toxicities, Troponin-I tests will be conducted at Screening and every 6 weeks thereafter. Alpha fetoprotein, TSH, PT, PTT and INR will also be collected at Screening and every 6 weeks thereafter. If a TSH result is > 20 mU/L additional thyroid tests to measure T3 and T4 will automatically be performed by the central laboratory.

Qualified medical staff at the site will review, initial and date all local and central laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.1.1.

Table 4. Clinical Laboratory Tests

Note: Performed at every visit unless indicated otherwise.

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total Bilirubin**** Serum glutamic-pyruvic transaminase (SGPT/ALT)**** Serum glutamic-oxaloacetic transaminase (SGOT/AST)**** Alkaline phosphatase Creatine Phosphokinase (CPK) Sodium Potassium Calcium Inorganic phosphorus Uric acid Total protein Glucose Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate	Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Microscopic examination if dipstick results are positive Spot urine Protein:creatinine ratio (UPCR)*
Coagulation		
International normalized ratio (INR)** Partial thromboplastin time (PTT)** Prothrombin time (PT)**		
	Special Chemistries	
	Cardiac troponin-I** Thyroid Stimulating Hormone (TSH)** T3/T4*** Alpha fetoprotein**	

* Collected at Screening and at Day 1 of every 3 weeks.

** Collected at Screening and every 6 weeks.

*** Performed if abnormal TSH > 20 mU/L.

**** For subjects in Japan only, collected at Day 4 of Weeks 1 and 2.

Multiple Gated Acquisition Scan (MUGA)/Echocardiogram

To monitor cardiac dysfunction, a MUGA or echocardiogram will be completed at Screening, on Day 1 of every 12 weeks, and at the Final Visit if not conducted within the

last 4 weeks. A qualified physician will sign and date the MUGA/echocardiogram scan reports, determine if any findings outside normal physiological variation are clinically significant and document this on the appropriate eCRF.

Tumor Assessments

A CT scan of the full chest and abdomen (with image of liver and adrenal glands) will be performed for all tumor assessments at Screening, at the end of every 6 weeks following Study Day 1 until Week 42, and then at the end of every 9 weeks thereafter (i.e., end of Week 51, end of Week 60, etc.) and at the Final Visit, if not performed within the last 4 weeks. If the subject discontinues from the study prior to the end of Week 6 scan, then a CT scan should be performed as close as possible to the end of Week 6. If the subject is unable to undergo CT with IV contrast due to allergy or renal insufficiency, a non-contrast CT or an MRI may be performed. Scheduled tumor assessments should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessments. Subjects will continue to be monitored by the same methodology unless evidence of tumor metastasis warrants otherwise.

In addition to being reviewed by the Investigator and on site staff, radiographic scans will be sent to a central imaging center, Synarc, for archiving. Synarc will provide instructions for preparation and shipment of images. Radiology scans may be assessed by the central imaging center if deemed appropriate by the Sponsor.

Changes in measurable lesions over the course of therapy will be assessed using RECIST (version 1.1) as described in Appendix C.[14]

Quality of Life

To assess the subject's quality of life, the Functional Assessment of Cancer Therapy Hepatobiliary (FACT-Hep),[18] Skin Toxicity Question (STQ), and European Quality of Life-5 Dimensions (EQ 5D)[19] questionnaires (Appendix F, Appendix G and Appendix H, respectively) will be administered at: Screening, Day 1 of every 3 weeks (i.e., Day 1 of

Week 4, Day 1 of Week 7, Day 1 of Week 10, etc.), Final Visit and at the Follow-up Visit. The subject will complete a paper CRF of the quality of life questionnaires. Site personnel should check the forms returned by the subject for completeness before the subject leaves the clinic. If the subject is unable to complete the form, qualified site personnel may administer the questionnaires via interview and complete the forms for the subject.

The FACT-Hep is a 45-item validated questionnaire that was developed to assess health-related quality of life among patients with hepatobiliary cancers. Nine scale scores can be calculated from the FACT-Hep: physical well-being, social/family well-being, emotional well-being, functional well-being, trial outcome index, FACT-G total score, hepatobiliary subscale, FACT Hepatobiliary Symptom Index 8 (FHSI-8) symptom score, and the FACT-Hep total score.

The Skin Toxicity Question is a single item question selected from the FACIT (developer of the FACT-Hep) item bank to assess the impact of skin toxicity on the subject's ability to work or engage in hobbies. Skin toxicity is a common adverse event among certain multi-kinase inhibitors but it is not assessed by the FACT-Hep which was developed and validated (1997-1998) ten years before the first targeted therapy was approved by the FDA for the treatment of HCC in 2007.

The EuroQol 5 Dimensions (EQ-5D) is a generic preference instrument that has been validated in numerous populations. The EQ-5D is composed of 5 questions that can be converted into a utility score for use in an economic evaluation to adjust life-years gained by the subject's health-related quality of life. The EQ-5D also contains a visual analog scale (VAS) to assess the subject's overall health.

Health Resource Utilization Questionnaire

A health resource utilization questionnaire (HRUQ) will be administered by interview to the subject by qualified site staff at Screening, Day 1 of every 3 weeks (i.e., Day 1 of Week 4, Day 1 of Week 7, Day 1 of Week 10, etc.), Final Visit and at the Follow-up Visit

including but not limited to hospitalizations, use of assisted care, etc. The site will complete a paper CRF for this questionnaire.

Randomization and Subject Number Assignment

The site will contact the IVRS/IWRS to obtain a screening (subject) number once the subject has signed the informed consent **and** a study-specific procedure has been performed (i.e., central labs drawn, MUGA performed, etc.). Once the screening number is assigned, if the subject is not randomized into the study, the reason for screen failure will be documented.

Subjects who complete all Screening procedures and meet the eligibility criteria will proceed to randomization. The results of the HBsAg test performed by the central laboratory, not the information collected from medical history, must be used to stratify the subject in IVRS/IWRS. If a subject has concurrent HBV and HCV infection, the subject will be included in the HBV group. The site will access the system on or prior to the subject's Study Day 1 visit and a unique randomization number will be provided.

Dispensation of Study Drug

During randomization in IVRS/IWRS, subjects will be assigned to receive linifanib or sorafenib. The IVRS/IWRS will assign every bottle of linifanib (and blister pack/bottle of sorafenib where supplied by Abbott) to be dispensed to a subject during the study. Prior to each scheduled visit, site personnel must contact IVRS/IWRS for the next bottle number assignment. Linifanib and sorafenib (where supplied by Abbott) cannot be dispensed or administered without contacting the IVRS/IWRS. Abbott or designee will provide specific instructions on the use of IVRS/IWRS.

Subjects randomized to receive linifanib or sorafenib (where supplied by Abbott) will receive sufficient quantities for 21 days of administration.

Abbott will only supply sorafenib where local regulations require. Where not supplied by Abbott, sorafenib should be obtained commercially.

Post Treatment Assessments

Post-treatment assessments will be collected via IVRS/IWRS at monthly intervals (or as requested by sponsor to support data analysis) after the last study visit until the endpoint of death or until the subject has become lost-to follow-up or until study termination by Abbott.

All subjects will be followed for survival information (i.e., the date and cause of death) unless the subject requests to be withdrawn specifically from study survival follow-up; this request must be documented in the subject's medical record and signed by the Investigator.

If known, post-treatment anti-cancer therapies, dates of initiation, and end dates should be reported. Additionally, if the subject discontinued the study for any reason other than disease progression, if known, the date of disease progression should be reported.

Additional heath resource utilization information will be collected via the IVRS/IWRS post study treatment, including but not limited to hospitalizations, use of assisted care, etc.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis

If PG testing is performed, results from individual subjects will be kept coded and confidential and will not be given to anyone not directly involved with this research study. Abbott will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. Samples will be coded so that subject identities will not be available to the scientists conducting the genotyping analyses. Individual subject results will not be provided to the Investigator so that neither the subject nor the Investigator will have knowledge of specific subject genotypes. Abbott will keep the DNA samples until destroyed by Abbott when this research is completed. These samples will not be stored longer than 20 years.

Pharmacogenetic variables are discussed in Section 5.3.7.

Collection of Pharmacogenetic Samples (Optional)

One 4 mL whole blood sample for DNA isolation will be collected on Study Day 1 from each subject who consents to provide samples for pharmacogenetic analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Whole blood will be collected by standard phlebotomy techniques as described below:

- The sample collection tubes will be appropriately labeled, with the protocol number, subject number, and study day and/or collection date.
- Collect approximately 4 mL of blood into an appropriately labeled EDTA tube.
- Immediately invert the collection tube 8 to 10 times to reduce the likelihood of clot formation.
- Store samples at –20°C or colder within 30 minutes of the blood draw until shipped/transported to the central laboratory on dry ice sufficient to last during shipment/transport. Samples should not be allowed to thaw prior to arrival at the central laboratory.

Shipment of Pharmacogenetic Samples

The central laboratory will provide instructions for shipping and an inventory sheet to be completed for samples shipped. Samples and the inventory sheet should be batch shipped to central laboratory on dry ice sufficient for 3 days.

5.3.1.3 Samples for Pharmacodynamic Analysis

Pharmacodynamic variables are discussed in Section 5.3.6.

Collection of Plasma Marker Samples

Approximately 12 mL (Study Day 1) or 6 mL (all other timepoints) of blood will be collected by venipuncture into one or two 6 mL EDTA tubes as appropriate in conjunction with clinical lab blood draws on Study Day 1, Day 1 of Weeks 2 and 3, every

6 weeks (i.e., Day 1 of Week 7, Day 1 of Week 13, etc.) and at the Final Visit. The date and time of blood collection will be recorded on the paper CRF. The complete process of centrifugation, transfer to cryovial and freezing should be accomplished in less than 1 hour from blood draw. The collection should be performed as described below.

- Collect the blood sample into a 6 mL EDTA tube (will require (2) 6 mL EDTA tubes on Study Day 1).
- Immediately invert the collection tube 8 to 10 times to reduce the likelihood of clot formation.
- Within 20 minutes, centrifuge sample at 1100 to 1300 × g for 10 minutes at 2° to 8°C.
- Immediately transfer plasma into appropriately labeled cryovials according to the following:
    - Fill a 1.2 mL cryovial (PlGF sample) with sufficient plasma to reach the 0.5 mL hash mark.
    - Evenly transfer the remaining plasma into two (2) 2 mL cryovials (proteomic samples). This will require four (4) 2 mL cyrovials on Study Day 1.
- Samples should be frozen immediately and stored at/or below –70°C until shipment.

Archived Tissue Collection (Optional)

For those subjects who consent and if available, archived tissue samples should be obtained once the subject has been randomized into the study.

From each representative formalin fixed paraffin embedded tumor tissue, the local pathology laboratory should apply 10 slices of tissue with a thickness of approximately 4 to 6 microns and 5 slices of tissue with a thickness of approximately 10 microns to positively charged slides to be used for IHC, mutational and FISH analysis. Therefore, a minimum of 15 slices of tissue sections should be collected from each subject block. In

cases where there is not enough appropriate tissue available to provide these sections, the Investigator will communicate with the pathology laboratory to determine the maximum number of slides that can be provided and relay that information to Abbott (contact information provided below) prior to slide preparation. Alternatively, the site can send the biopsy block and Abbott or a designated contract research organization (CRO) will prepare the appropriate slides.

Abbott Contact for Archived Tissue Samples

Peter J. Ansell or Evelyn McKeegan
100 Abbott Park Road
Abbott Park, IL 60064
Phone: (847) 935-1222 or (847) 935-1969
Email: peter.ansell@abbott.com or evelyn.mckeegan@abbott.com

To ensure optimal sampling, two quality control slides must also be prepared by the pathology laboratory and included in the shipment of slides to Abbott. These quality control slides will be representative of the beginning and of the end of the tissue section. These slides are to be stained using Hematoxylin and Eosin (H&E) and reviewed by the local pathologist to ensure the diagnostic quality of viable tumor and normal cells (i.e., large regions of necrosis or areas composed primarily of fibrous connective tissue or adipose tissue are not the predominant feature). The remaining tissue prepared for the unstained slides will be procured from the sections closest to the section that is of adequate diagnostic quality.

Included with each shipment should be a copy of the pathology report, with all specific subject identification other than subject number information removed or defaced, and a completed shipment inventory form. Slide boxes should be labeled with study drug number, sample matrix (tissue), protocol number, subject number and collection date. Slide boxes should be packaged using suitable shipping materials and sent to the central laboratory at ambient temperature.

Shipment of Pharmacodynamic Samples

Plasma Marker Samples

The central laboratory will provide instructions for shipping and an inventory sheet to be completed for samples shipped. Samples and the inventory sheet may be batch shipped to central laboratory on dry ice sufficient for 3 days.

Archived Tissue Samples

Included with each shipment should be a copy of the pathology report with confidential subject information redacted and a completed shipment inventory sheet. The central laboratory will provide instructions for shipping and an inventory sheet to be completed for samples shipped.

5.3.2 Drug Concentration Measurements

Pharmacokinetic variables are discussed in Section 5.3.5.

5.3.2.1 Collection of Samples for Analysis

Blood samples for linifanib determinations (collected only from those subjects randomized to receive linifanib) will be collected by venipuncture into 3 mL potassium EDTA vacutainers in conjunction with clinical lab blood draws (if possible) on Day 1 of the following visits (Table 3):

- Week 2
- Week 3
- Week 7
- Week 13
- Week 25
- Week 37
- Week 52

Samples should not be collected when subjects are on a dose interruption. Sufficient blood will be collected to produce approximately 1.5 mL of plasma for each sample.

An additional sample should be collected for any subject randomized to linifanib who experiences an adverse event of encephalopathy/ hepatic encephalopathy. Every effort should be made to obtain a sample at the onset of the event. If the subject is on a dose interruption at the onset of the event, a sample should not be collected.

The date and time of collection of each blood sample will be recorded. The date and time of the last 2 doses of linifanib and compliance to fasting administration (as defined in Section 5.5.4) for the last 2 doses will be confirmed with the subject and captured on the paper CRF including subjects who had an additional PK sample drawn as a result of an event of encephalopathy/ hepatic encephalopathy.

5.3.2.2 Handling/Processing of Samples

The complete process of centrifugation, transfer to polypropylene tubes and freezing should be accomplished within 2 hours from blood draw. The processing of PK samples should be performed as described below.

- Immediately invert the collection tube 8 to 10 times.
- Centrifuge sample at 1100 to 1300 × g for 10 minutes at 2° to 8°C.
- Transfer plasma into an appropriately labeled screw-capped polypropylene tube and freeze at –20°C.
- Store sample at/or below –20°C until shipment to the central lab.

5.3.2.3 Disposition of Samples

The central laboratory will provide instructions for shipping and an inventory sheet to be completed for samples shipped. Samples may be batch shipped to the central laboratory on dry ice sufficient for 3 days.

5.3.2.4 Measurement Methods

Plasma concentrations of linifanib will be determined under the supervision of the Drug Analysis Department at Abbott.

5.3.3 Efficacy Variables

The primary endpoint of this study will be overall survival. The secondary endpoints of this study will be time to progression and objective response rate. The tertiary endpoints will be progression free survival and QoL.

5.3.4 Safety Variables

Abbott will assess adverse events, laboratory data, and vital signs throughout the study. Adverse events will be assessed according to NCI CTCAE Version 4.0.[15]

5.3.5 Pharmacokinetic Variables

Collection and shipment of pharmacokinetic samples is discussed in Section 5.3.2.

For subjects randomized to linifanib group, an analysis will be performed using a nonlinear mixed-effect population modeling approach with NONMEM software to describe the disposition of linifanib, to identify significant covariates and explore relationship between pharmacokinetics and pharmacodynamics by combining data from this study with other linifanib clinical studies.

Additional analyses may be performed if useful in the interpretation of the data.

Abbott or a designated laboratory will store the pharmacokinetic samples in a secure storage space with adequate measures to protect confidentiality. To increase confidence in trends, remaining sample aliquots may be used to perform replicate tests, or sample analysis at additional time points for tests currently identified in the protocol. Upon completion of this research Abbott or a designated laboratory will destroy the samples.

5.3.6 Pharmacodynamic Variables

Collection and shipment of pharmacodynamic samples is discussed in Section 5.3.1.3.

Several putative biomarkers of efficacy and response will be evaluated with the goal of defining the relationship between drug concentration and disease status. These markers will include examination of plasma components such as nucleic acids and proteins/peptides. If warranted additional studies may include quantification and/or analysis of the methylation and mutational status of circulating nucleic acids including DNA.

Tumor tissue obtained by biopsy may be analyzed for tumor DNA methylation/mutation and copy number as well as expression of genes (protein, miRNA and mRNA) including but not limited to those involved in angiogenesis and cell cycle.

Abbott or a designated laboratory will store the biospecimens in a secure storage space with adequate measures to protect confidentiality. To increase confidence in trends, remaining sample aliquots may be used to perform replicate tests, or sample analysis at additional time points for tests currently identified in the protocol. Remaining samples will be anonymized and banked for potential use in diagnostic test development efforts. The samples will be retained while research with linifanib continues or up to 20 years. Upon completion of the research Abbott or a designated laboratory will destroy the samples.

5.3.7 Pharmacogenetic Variables

Collection and shipment of pharmacogenetic samples is discussed in Section 5.3.1.2.

DNA samples from this protocol may be used to assess the influence of genetic variants on pharmacokinetics, safety or efficacy. For example, polymorphisms in genes that encode drug metabolizing enzymes or drug transport proteins may be assessed for their influence on linifanib pharmacokinetics. Genetic variants of potential linifanib targets (such as VEGF or PDGF RTKs) may also be assessed. The genes which may be studied in the course of these investigations are numerous and some may still be phenotypically insufficiently characterized or as yet unknown.

The samples may be analyzed as part of a multicenter, multi-study project to identify genetic factors involved in the response to linifanib or drugs of this class. In addition, these samples may be used to study genes associated with the disease under study and potential new targets for treatment of the cancer. The samples may also be used for development of a diagnostic test for drug response. The results of pharmacogenetic analyses may not be reported with the study summary.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

5.4.1.1 Discontinuation of Study Drug

Each subject has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a subject from study drug at any time for any reason if the Investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol.

Each subject will be withdrawn from the study if any of the following occur:

- The subject or subject's legally acceptable representative withdraws consent. All subjects will be followed for survival information unless the subject requests to be withdrawn specifically from study survival follow-up; this request must be documented in the subject's medical record and signed by the Investigator.

- The subject experiences unacceptable toxicities deemed possibly or probably related to drug that have not resolved to at least Grade 1 or to the subject's baseline status within 21 days of onset.
- The subject experiences disease progression (as defined by RECIST version 1.1).
    - If the subject discontinues for symptomatic deterioration, every effort should be made to document objective progression even after discontinuation of treatment.
- The subject requires cancer-related surgery or radiation therapy, or alternate antineoplastic agents during the study period.
- Significant noncompliance with the protocol that could impact subject safety or data integrity.
- The Investigator believes it is in the best interest of the subject.
- The subject has a positive pregnancy test result.

5.4.1.2 Study Drug Discontinuation Procedures

When a subject discontinues study treatment, the Investigator must report the discontinuation to the IVRS/IWRS system within 3 working days of the subject's Final Visit.

A Final Visit will be conducted (preferably prior to the initiation of another anti-cancer therapy). However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment. At the Final Visit, the reason(s) for discontinuation from the study must be recorded. A symptom-directed physical examination, (including body weight), vital signs measurement, performance status assessment, tumor assessment, MUGA/echocardiogram and ECG (if not performed within the last 4 weeks), QoL assessment, laboratory analyses, collection of unused study

drug and an assessment of adverse events will be performed. Additional blood samples for pharmacodynamic monitoring will also be collected.

All subjects will have a Follow-up Visit approximately 30 days after the last dose of study drug (linifanib or sorafenib). This Follow-Up Visit does not need to be performed for subjects who have had a Final Visit conducted ≥ 30 days after the last dose of study drug.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

Discontinued subjects will not be replaced.

5.4.2 Discontinuation of Entire Study

Active subjects randomized to linifanib or sorafenib will continue on study treatment until disease progression or toxicity prohibits continuation, or for a period up to 15 months following the occurrence of the 667th event of death. For subjects randomized to receive linifanib, Abbott and the Investigator will develop a plan to provide linifanib. As sorafenib is commercially available, Abbott will not provide sorafenib once the entire study is discontinued.

Survival (e.g., the date and cause of death) and post-treatment information (including therapies received and health resource utilization questions) will be collected via IVRS/IWRS at monthly intervals (or as requested by sponsor to support data analysis) after the last study visit until the endpoint of death or until the subject has become lost to follow-up or until study termination by Abbott.

Abbott may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable

cause, after providing written notice to Abbott in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns.

The following procedures for discontinuation will be followed:

- If the Sponsor has decided to prematurely discontinue the study, the Sponsor will promptly notify in writing the Investigator as well as regulatory authorities of the decision and give detailed reasons for the discontinuation.
- The Investigator must promptly notify the IRB/IEC and give detailed reasons for the discontinuation.
- The Investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of the treatment regimen, if applicable, by other appropriate regimens.

5.5 Treatments

5.5.1 Treatments Administered

5.5.1.1 Sorafenib Treatment

Subjects randomized to the sorafenib group will be trained to self-administer 400 mg BID sorafenib per the locally approved product label or applicable Summary of Product Characteristics.

5.5.1.2 Linifanib Treatment

Subjects randomized to the linifanib group will be trained to self-administer linifanib tablets orally with at least 120 mL of water once daily under fasting conditions in the evening. Fasting conditions are defined as no food or beverage consumption (except water and scheduled concomitant medications) for a minimum of 2 hours before dosing with linifanib and for a minimum of 2 hours after dosing with linifanib.

Subjects will receive 17.5 mg linifanib QD. Subjects will remain at this dose for the duration of the study unless a dose reduction is required (Section 6.7.1).

5.5.4 Selection and Timing of Dose for Each Subject

All subjects randomized to the sorafenib group will receive 400 mg BID. Dose modifications will be based on the locally approved product label or applicable Summary of Product Characteristics. In countries where sorafenib is not approved for HCC, dose modifications will be based on the guidance provided in the US product label.[8]

All subjects randomized to the linifanib group will be trained to self-administer an oral dose of 17.5 mg with at least 120 mL of water under fasting conditions in the evening. Fasting conditions are defined as no food or beverage consumption (except water and scheduled concomitant medications) for a minimum of 2 hours before dosing with linifanib and a minimum of 2 hours after dosing with linifanib. Subjects will be provided self-administration instructions. Dose modification will occur as described in Section 6.7.1.

6.7 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the Investigator according to the National Cancer Institute (NCI) common toxicity criteria version 4.0.[15] Linifanib Toxicity Management Guidelines are detailed in Appendix D.

6.7.1 Linifanib Dose Reductions and Delays

If a subject experiences an adverse event attributable to study drug and not the underlying disease, study drug may be either:

- interrupted for a drug holiday up to 21 days

  and/or

- the dose may be reduced.

In addition, if a subject experiences an increase in bilirubin or AST by at least 1 Grade level to Grade 2 or higher during Study Days 1 through 15, even if it is not considered an adverse event, the study drug must be interrupted for 7 days (See Appendix D, Table 23).

If a dose reduction of study drug is needed, the dose will decrease by 5 mg for the first reduction followed by 2.5 mg for all subsequent reductions (Table 6). The IVRS/IWRS will calculate the appropriate dose to be used for a subject receiving a dose reduction and

dispense new study medication if applicable. If a subject requires more than 3 dose reductions and the Investigator feels the subject is continuing to receive benefit from treatment with study drug, further dosing considerations should be discussed with the Abbott Medical Monitor listed in Section 6.5.

Table 6. Linifanib Dose and Reductions

Starting Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
17.5 mg	12.5 mg	10 mg	7.5 mg

If a drug interruption is needed, the subject will continue to have study visits as planned; however PK samples will not be drawn. PD samples should be drawn as scheduled. Study visits and procedures will not be modified, but will continue to follow the study schedule as outlined in Section 5.3. Additionally, unscheduled visits to follow the subject during the study drug interruption may be added at the discretion of the Investigator. Per the Investigator's discretion, the subject may return to the current dose or may receive a dose reduction following the dose interruption.

Study drug interruptions for events that are clearly not related to the study drug (e.g., planned surgical procedures or acute viral illnesses) should not necessitate a dose reduction. The timing of dose resumption should be at the discretion of the study Investigator. Linifanib dose increases are not permitted.

6.7.2 Sorafenib Dose Reductions and Delays

Toxicities attributable to sorafenib should be managed according to the locally approved product label or applicable Summary of Product Characteristics. In non-EU countries where sorafenib is not approved for HCC, the guidance in the US product label should be followed.[8]

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05.

The primary, secondary and tertiary efficacy analyses will be performed on all randomized subjects. The date of randomization (enrollment) is defined as the date that the IVRS/IWRS issues a randomization number.

Safety analyses will be performed on all subjects who receive at least 1 dose of the study drug (linifanib or sorafenib).

8.1.1 Baseline Characteristics

All baseline summary statistics and analyses will be based on characteristics obtained prior to the first dose of study drug (or randomization for non-treated subjects). Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to the first dose of study drug. Baseline characteristics data will be summarized and compared between the two treatment groups.

8.1.1.1 Demographics and Baseline Characteristics

Age, height and weight will be summarized with means, standard deviation and range. For the following parameters: race, smoking history, region, performance status, vascular invasion or extrahepatic spread (i.e., portal invasion, N1 [regional lymph node metastasis] or M1 [distant metastasis]) (yes versus no), HCC etiologies (Hepatitis B

infection, Hepatitis C infection, alcoholic cirrhosis, other), alpha-feto protein (AFP) (low versus normal versus high) and gender frequencies and percentages will be computed and compared between the two treatment groups using Fisher's exact test.

8.1.1.2 Medical History

Frequencies and percentages will be computed for each medical history parameter.

8.1.2 Efficacy Endpoints

8.1.2.1 Primary Efficacy Endpoint

The primary efficacy analysis will be a comparison of overall survival (OS) distributions between the linifanib and sorafenib treatment groups.

Time to death for a given subject will be defined as the number of days from the date that the subject is randomized to the date of the subject's death. All events of death (up to the 667th death for final analysis) will be included, regardless of whether the event occurs while the subject is still taking study drug, or after the subject discontinues study drug. If a subject has not died, then the data will be censored at the date when the subject is last known to be alive.

8.1.2.2 Secondary Efficacy Endpoints

Secondary efficacy analyses comparing the effects of linifanib versus sorafenib will also be performed on time to progression (TTP) and objective response rate (ORR).

Time to progression will be defined as the number of days from the date of randomization to the date of earliest disease progression, per RECIST (version 1.1). All disease progression will be included regardless of whether the event occurs while the subject is taking the study drug or has previously discontinued the study drug. If the subject does not experience disease progression, then the data will be censored at the date of last radiographic tumor assessment. If the subject does not experience disease

progression and does not have any post-baseline radiographic tumor assessments, then the subject will be censored at the date of randomization.

Objective response rate is defined as the proportion of subjects with confirmed complete or partial response per RECIST (version 1.1). All complete or partial responses will require confirmation on visits ≥ 4 weeks apart, even though confirmation of response is not required per RECIST v1.1 (except in non-randomized studies in which response rate is the primary endpoint).

8.1.2.3 Tertiary Efficacy Endpoints

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses comparing the effects of linifanib versus sorafenib on progression-free survival (PFS) and QoL (FACT-Hep, STQ and EQ-5D) will be performed.

For a given subject, PFS will be defined as the number of days from the date that the subject is randomized to the date the subject experiences an event of disease progression per RECIST (version 1.1) or to the date of death (all causes of mortality) if disease progression is not reached. All events of disease progression will be included, regardless of whether the event occurs while the subject is still taking study drug or has previously discontinued study drug. All events of death will be included for subjects who have not experienced disease progression provided the death occurred within 42 days of the last radiographic tumor assessment. If the subject does not have an event of disease progression nor has the subject died, the subject's data will be censored at the date of the subject's last available radiographic tumor assessment.

8.1.3 Safety Assessments

The safety of linifanib will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

8.1.4 Timing of Efficacy Analyses and Safety Evaluations

When the 667th death occurs, there will be a final review of the eCRF data. When the data is reviewed for completeness and all data management quality assurance (QA) and quality control (QC) procedures are performed, the randomization schedule will be released and clinical database data will be extracted for documentation and statistical analyses of the efficacy and safety data. For all efficacy analyses, the data cutoff date will be the date of the occurrence of the 667th death. For the analysis of overall survival (OS), if a subject has not died on or before the 'cutoff' date, and there is data (study visit, survival follow up, etc.) confirming that the subject is dead or alive after the 'cutoff' date, the subject will be censored at the 'cutoff' date. If a subject is last known alive prior to or on the cutoff date, the subject will be censored at the date the subject is last known alive. For the analyses of time to progression (TTP) and progression-free survival (PFS), if the subject does not have an event of disease progression (for TTP and PFS) and death (for PFS only) on or before the 'cutoff' date, the subject's data will be censored at the date of the subject's last available radiographic tumor assessment on or before the 'cutoff' date with the following exception: if there is any radiographic tumor assessment after the 'cutoff' date demonstrating the evidence of progression free per RECIST v1.1, the censoring date will be set to the 'cutoff' date

For safety analyses, the exact data cutoff date will be further documented in the statistical analysis plan (SAP).

The clinical study report (CSR) will be written based on the results from the above analyses.

Overall survival will be collected on all subjects for up to 5 years after they discontinue from the study. After all survival data have been collected and entered into the clinical database, the clinical database data will be extracted once again for documentation and a "Final Analysis" will be performed on this dataset.

8.1.5 Primary Analysis of Efficacy

8.1.5.1 Overall Survival

The distribution of the time to death will be estimated for each treatment group using Kaplan-Meier methodology. Median survival time will be estimated and 95% confidence interval for the estimated median survival time will be presented for each treatment group. Both non-inferiority and superiority hypotheses will be tested for primary efficacy endpoint overall survival using the Cox proportional hazard model with treatment as a factor, stratified by region (Non-Asia versus Japan versus Rest of Asia), ECOG performance status (0 versus 1), vascular invasion or extrahepatic spread (i.e., portal invasion, N1 [regional lymph node metastasis] or M1 [distant metastasis]) (yes versus no), and Hepatitis B infection (yes versus no). Non-inferiority for overall survival will be tested first with a non-inferiority margin of 1.0491. If non-inferiority is declared for overall survival, then superiority will be tested for overall survival. Hazard ratio and the corresponding confidence interval will be obtained from the stratified Cox proportional hazard model.

If the study is not stopped for superior efficacy at the interim analysis, non-inferiority will be declared at the final analysis if the upper limit of the 2-sided 95.1% confidence interval for hazard ratio is ≤ 1.0491, which means that linifanib preserves at least 75% of the sorafenib treatment effect as observed in the sorafenib SHARP[9] and Asia-Pacific[10] trials. Furthermore, superiority will be declared at the final analysis if the upper limit of the 2-sided 95.1% confidence interval for hazard ratio is ≤ 1.0 (corresponding to one-sided superiority test *P* value ≤ 0.0245, Section 8.1.10).

Choice of Non-inferiority Margin

The non-inferiority margin (or cutoff) of 1.0491 is chosen based on the sorafenib SHARP[9] trial and Asia-Pacific[10] trial data. In the SHARP trial, the estimated hazard ratio (95% CI) for sorafenib versus placebo is 0.69 (0.55, 0.87). In the Asia-Pacific trial, the estimated hazard ratio (95% CI) for sorafenib versus placebo is 0.68 (0.50, 0.93). Using meta analysis method proposed by Whitehead et al[25] and Parmar MK et al,[22] the pooled

hazard ratio and the 2-sided 95% CI are 0.6865 (0.5709, 0.8255). Using the 95% CI lower limit method on log hazard ratio as described in Rothmann et al,[23] the non-inferiority margin corresponding to 75% retention of sorafenib effect is calculated as 1.0491. If at the final analysis the 2-sided 95.1% CI for the hazard ratio (linifanib/sorafenib) lies entirely beneath 1.0491, non-inferiority of linifanib to sorafenib is inferred – a better than 75% retention of sorafenib effect by linifanib is demonstrated. Although medians are 'crude' single number summaries and may not be reflective of the entire survival curve, the goal in this study is to retain at least 75% of the benefit that sorafenib had over placebo. On the median survival time scale, this NI margin of 1.0491 corresponds to at least 2.1 months survival benefit with linifanib compared to placebo, a duration of survival benefit generally considered to be clinically meaningful.

8.1.6 Secondary Analyses of Efficacy

If the primary efficacy analysis is statistically significant for the superiority test, then secondary efficacy endpoints will be tested, and *P* values for the secondary efficacy analyses will be subject to multiple comparison adjustments using the fixed-sequence testing method, with analyses performed in the following order: (1) time to progression, (2) objective response rate. If the TTP analysis does not achieve statistical significance at the $\alpha = 0.05$ level, then statistical significance will not be declared for ORR, regardless of the observed *P* value. Appropriate α-spending function will be used to for the secondary analyses of efficacy to control the overall Type I error rate. Details on the α-spending function will be further documented in the Statistical Analysis Plan.

8.1.6.1 Time to Progression

The distribution of TTP will be estimated for each treatment group using Kaplan-Meier methodology. Median time TTP will be estimated and 95% confidence interval for median time TTP will be presented for each treatment group. Superiority of linifanib to sorafenib will be tested for TTP using the Cox proportional hazard model with treatment as a factor, stratified by region (Non-Asia versus Japan versus Rest of Asia), ECOG performance status (0 versus 1), vascular invasion or extrahepatic spread (yes versus no),

and Hepatitis B infection (yes versus no). Hazard ratio and the corresponding 95% confidence interval will be obtained from the stratified Cox proportional hazard model.

8.1.6.2 Objective Response Rate

The objective response rate (proportion of subjects with a confirmed complete or partial objective response based on RECIST (version 1.1)[14] in Appendix C) will be compared between the two treatment groups using Cochran-Mantel-Haenszel (CMH) test, stratified by region (Non-Asia versus Japan versus Rest of Asia), ECOG performance status (0 versus 1), vascular invasion or extrahepatic spread (yes versus no), and Hepatitis B infection (yes versus no). In addition, the objective response rate and the corresponding 95% confidence interval will be obtained for each treatment group. All subjects who are randomized will be included in the analysis.

8.1.7 Tertiary Analyses of Efficacy

8.1.7.1 Progression Free Survival

The distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology. Median time PFS will be estimated and 95% confidence interval for median time PFS will be presented for each treatment group. Superiority of linifanib to sorafenib will be tested for PFS using the Cox proportional hazard model with treatment as a factor, stratified by region (Non-Asia versus Japan versus Rest of Asia), ECOG performance status (0 versus 1), vascular invasion or extrahepatic spread (yes versus no), and Hepatitis B infection (yes versus no). Hazard ratio and the corresponding 95% confidence interval will be obtained from the stratified Cox proportional hazard model.

8.1.7.2 Quality of Life

Randomized subjects who do not have baseline measurement or any post-baseline measurements will not be included in any of the analyses. Post-baseline measurements more than 30 days after the last dose of study drug will not be included.

Descriptive statistics will be calculated for all scales of the FACT-Hep, the STQ, the EQ-5D utility score, and the EQ-5D VAS score including mean change from baseline to each visit as well as the final visit by treatment arm. Comparisons based on mean changes will be investigated using appropriate statistical methods including but not limited to last observation carried forward (LOCF), ANCOVA, and mixed models.

Descriptive statistics will be calculated for the HRUQ including change from baseline to each visit and final visit by treatment arm for the number of visits.

8.1.8 Additional Efficacy Analyses

In addition to the stratified Cox proportional hazards model for the primary and secondary efficacy endpoints, the following analyses will be performed for the comparison of OS and TTP between linifanib and sorafenib treatment groups.

- Stratified (by the 4 randomization stratification factors) log-rank test for OS and TTP
- Un-stratified log-rank test for OS and TTP
- Covariate adjusted (by the 4 randomization stratification factors) Cox proportional hazard model for OS and TTP

For overall survival and TTP, additional analyses may also be performed, such as (1) including only data and events occurring on treatment or within 30 days of the last dose of study drug, (2) subgroup analysis by region (Non-Asia versus Japan versus Rest of Asia), ECOG performance status (0 versus 1), vascular invasion (yes versus no), extrahepatic spread (yes versus no), vascular invasion or extrahepatic spread (yes versus no), Hepatitis B infection (yes versus no), Hepatitis C infection (yes versus no) and others.

Alternative statistical analyses may be performed if deemed as necessary and helpful in understanding the drug effect.

8.1.9 Independent Data Monitoring Committee

Interim analyses results will be reviewed by an Independent Data Monitoring Committee (IDMC). A separate charter will be created to provide detailed descriptions of the anticipated schedule of the interim analyses and the IDMC meeting. The IDMC membership and responsibilities will also be documented in the charter. The IDMC will receive an interim analysis summary, divided by treatment group, which includes enrollment and baseline characteristics, safety and efficacy data. After review, the IDMC will communicate its recommendations to Abbott on whether to continue, modify or discontinue the study. Recommendations to discontinue the trial due to efficacy or for futility are subject to the predefined interim analysis plans.

8.1.10 Interim Analyses

A total of two formal interim analyses will be performed.

The first interim analysis will be performed for futility only, using overall survival as the endpoint. It will be performed when approximately 200 deaths (30% of the required events) are observed. The Lan-DeMets spending function will be used to derive the futility stopping boundary. In addition, time to progression and objective response rate may also be evaluated. The second interim analysis will be performed for both efficacy and futility, using OS as the endpoint. It will be performed when approximately 333 deaths (50% of the required events) are observed. The Lan-DeMets alpha spending function with an O'Brien Fleming boundary will be used to ensure that the one-sided false positive rate will be 0.025 or less for overall survival. Interim statistical analyses and summaries for presentation to the IDMC will be prepared by a CRO. Abbott personnel will not have access to the interim analyses prepared for the IDMC.

In making any decision to recommend discontinuation of the study (either for efficacy or futility) at the interim analyses, the IDMC shall be guided by a formal stopping rule based on the primary efficacy endpoint of overall survival. The O'Brien–Fleming boundaries at the interim analyses and the final analysis are tabulated below (Table 7).

The derivation of the futility boundary is based on a non-inferiority design with assumed true hazard ratio of 0.80 and NI margin of 1.0491.

Table 7. Stopping Boundaries at Interim and Final Analyses of Overall Survival

Analysis	Number of Observed Events	Efficacy Stopping Boundary	Futility Stopping Boundary
		One-sided *P* value	One-sided *P* value
1st Interim Analysis	200	N/A	≥ 0.8981
2nd Interim Analysis	333	≤ 0.0015	≥ 0.4646
Final Analysis	667	≤ 0.0245	

If the study is stopped at the interim analysis, the data cutoff date for final efficacy analyses will be the data cutoff date of the interim analysis.

8.1.11 Pharmacokinetic Statistical Analysis

For subjects randomized to the linifanib group, an analysis will be performed using a nonlinear mixed-effect population modeling approach with NONMEM software to describe the disposition of linifanib, to identify significant covariates and explore relationship between pharmacokinetics and pharmacodynamics by combining data from this study with other linifanib clinical studies.

8.1.12 Pharmacodynamic Statistical Analysis

Pharmacodynamic variables will be summarized as appropriate.

The relationship between drug concentrations and pharmacodynamic variables will be explored.

Additional analyses may be performed if useful.

8.1.13 Statistical Analysis of Safety

The safety of linifanib and sorafenib will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters. Subjects who are randomized but do not receive study drug will not be included in the analyses of safety.

Safety analysis results will be presented by treatment group (linifanib or sorafenib).

8.1.13.1 Duration of Study Drug

A summarization of the number of days subjects are exposed to study drug will be provided. The number and percentage of subjects with dose interruption, dose reduction, dose interruption or reduction will be summarized by treatment group. Dose intensity and average daily dose will also be summarized by treatment group.

8.1.13.2 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug. Analyses will not include those that have an onset greater than 30 days after the last dose of study drug.

Treatment emergent adverse events will be summarized by system organ class and preferred term according to the MedDRA adverse event coding dictionary.[21] The percentage of subjects experiencing an adverse event at a NCI CTCAE version 4.0[15] toxicity grade, and relationship to study drug will be provided.

Comparisons of the percentages of subjects experiencing an adverse event between linifanib and sorafenib will be performed using Fisher's exact test.

8.1.13.3 Serious Adverse Events

Serious adverse events will be summarized using the same methods as the Adverse Events described above.

8.1.13.4 Deaths

The number of subject deaths will be summarized for deaths occurring within 30 days of the last dose of study drug.

8.1.13.5 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, then an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included. At a given visit, the change from baseline will be compared between the two treatment groups using an analysis of variance (ANOVA) model with treatment group as the factor.

8.1.13.6 Analyses of Laboratory Data Using NCI CTCAE

Where applicable, blood chemistry and hematology determinations will be categorized according to NCI CTCAE version 4.0[15] grades, and shifts from baseline NCI CTCAE grades to maximum and final post-baseline grades will be assessed.

The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the last post-baseline measurement collected no more than 30 days after the last dose of study drug.

The number of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post baseline grades of 3 to 4 between linifanib and sorafenib will be summarized. The rate of subjects with shift from baseline grade 0-2 to grades 3-4 will be compared between the two treatment groups using Fisher's exact test. All treated subjects with baseline toxicity grade of 0-2 and post baseline grades will be included in this analysis.

8.1.13.7 Special Safety Evaluation of Linifanib among Japanese and Chinese Subjects

Special Safety Evaluation of Linifanib among Japanese Subjects

When there are six Japanese HCC subjects randomized to receive linifanib, the enrollment of Japanese subjects will be temporarily suspended until the safety evaluation is performed on these six Japanese subjects who receive linifanib. Assessment of Dose Limiting Toxicities in these subjects, as described in Appendix J will determine the analyses required. Once the analysis is complete and the safety is deemed acceptable, Japanese sites will be fully open to enrollment.

Special Safety Evaluation of Linifanib among Chinese Subjects

When there are six Chinese HCC subjects randomized to receive linifanib, the enrollment of Chinese subjects will be temporarily suspended until the safety evaluation is performed on these six Chinese subjects who receive linifanib. Assessment of Dose Limiting Toxicities in these subjects, as described in Appendix L will determine the analyses required. Once the analysis is complete and the safety is deemed acceptable, Chinese sites will be fully open to enrollment.

8.2 Determination of Sample Size

Assuming the true hazard ratio in favor of the linifanib group is 0.80, a total of 667 deaths will be needed for the study to have 80% power at one-sided α level of 0.025 to detect a statistically significant treatment effect for the linifanib group using the log rank test for overall survival. Two interim analyses, one for futility only and one for both efficacy and futility will be performed and reviewed by an Independent Data Monitoring Committee when approximately 200 deaths (30% of the required number of events) and 333 deaths (50% of the required number of events) are observed. The Lan DeMets alpha spending function with an O'Brien-Fleming boundary will be used to ensure that the one-sided false positive rate will be 0.025 or less for overall survival. Further assuming that the time to death on both treatment groups follows exponential survival distribution, a total of approximately 900 subjects will need to be enrolled into

the study during a 20 month period with maximal follow-up period of 35 months. Two hundred Chinese subjects are required per the SFDA and thus the sample size may increase to 1,100 pending the timing of the completion of the Chinese tolerability subset (Appendix L). Despite the possible sample size increase from 900 to 1,100, the time of the primary efficacy analysis is still defined as the date of the 667th death event.

The power of the study (with 667 events) corresponding to a range of possible true hazard ratios is tabulated below.

Power (for Superiority Test)	True HR
80%	0.80
68%	0.82
54%	0.84
46%	0.85

Using a non-inferiority test on the primary efficacy endpoint overall survival with a non-inferiority margin of 1.0491, the power of the study to declare non-inferiority is tabulated below for the same range of possible hazard ratios.

Power (for Non-Inferiority Test)	True HR
93%	0.80
88%	0.82
80%	0.84
74%	0.85

8.3 Randomization Methods

IVRS/IWRS will be utilized to randomize subjects. Before the study is initiated, directions for the IVRS/IWRS will be provided to each site. The investigational site will contact the IVRS/IWRS prior to the subject's Study Day 1 and a unique randomization number will be provided. The randomization numbers will assign subjects to either linifanib or sorafenib. Subjects will be randomized in a 1:1 ratio, with half of the subjects being randomized to the linifanib treatment group and the other half of the subjects being

randomized to the sorafenib group. Subject randomization will be stratified by three primary regions (Non-Asia versus Japan versus Rest of Asia), ECOG performance status (0 versus 1), vascular invasion or extrahepatic spread (yes versus no), and Hepatitis B infection (yes versus no). The results of the HBsAg test performed by the central laboratory, not the information collected from medical history, must be used to stratify the subject in the IVRS/IWRS. Subjects with concurrent Hepatitis B and Hepatitis C infection will be included in the Hepatitis B group. Additional breakdown of one or more of the primary regions may also be included. For statistical analyses, the additional regions will be incorporated into the appropriate primary region. The site will contact the system prior to the subject's Study Day 1 and a unique randomization number will be provided.

A subject randomization schedule will be generated by the Clinical Statistics Department at Abbott prior to the start of the study. A copy of all randomization schedules will be kept by the Clinical Statistics Department at Abbott and a copy will be forwarded to the IVRS/IWRS vendor.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (Director of the Site in Japan) and Abbott. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (Director of the Site in Japan) and Abbott. The Investigator will provide a final report to the IEC/IRB following conclusion of the study and will forward a copy of this report to Abbott or their representative.

The Investigator (Director of the Site in Japan) must retain any records related to the study according to local requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify Abbott to arrange alternative archiving options.

Abbott will select the signatory investigator from the Investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as

significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit or date of last follow-up contact, whichever is later.

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