ClinicalTrials.gov NCT #: NCT01556490

Study Title: Efficacy Evaluation of TheraSphere in Patients With Inoperable Liver Cancer (STOP-HCC)

Approved Document Date: 22 July 2019

Redacted Document Date: 28 April 2023

Protocol Number:	TS-103
Protocol Short Title:	STOP-HCC
Protocol Name:	A Phase III Clinical Trial of Intra-arterial Thera**S**phere® in the **T**reatment **o**f **P**atients with Unresectable Hepatocellular Carcinoma (**HCC**)
US Sponsor:	[redacted] BTG International Inc. [redacted]
Global Sponsor:	Biocompatibles UK Ltd [redacted]
Global Principal Investigator	[redacted]
US Medical Monitor	[redacted] Covance [redacted]
Protocol Medical Monitor	[redacted] Covance [redacted]
Device:	TheraSphere®, Yttrium-90 Glass Microspheres
FDA File #:	IDE 100322
CE Mark for EU sites only	CE 0123
Protocol Activation Date:	2011/03/09 (YYYY/MM/DD)

Amendments:	Version 2.0 2012/01/24 (YYYY/MM/DD) Version 3.0 2013/09/06 (YYYY/MM/DD) Version 4.0 2014/03/04 (YYYY/MM/DD) Version 4.1 2014/05/20 (YYYY/MM/DD) Version 5.0 2015/01/08 (YYYY/MM/DD) Version 6.0 2016/08/24 (YYYY/MM/DD) Version 6.1 2016/11/29 (YYYY/MM/DD) Version 7.0 2019/07/22 (YYYY/MM/DD)

PROTOCOL APPROVAL AND RELEASE SIGNATURE PAGE

Protocol Title: A Phase III Clinical Trial of Intra-arterial TheraSphere® in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (HCC)

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Protocol Approval Date: Version 1.0 2011/03/09 (YYYY/MM/DD)
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Version 6.0 2016/08/24 (YYYY/MM/DD)
Version 6.1 2016/11/29 (YYYY/MM/DD)
Version 7.0 2019/07/22 (YYYY/MM/DD)

The above-referenced protocol was reviewed and approved for release by the following:

Approver	Signature
Principal Investigator: [redacted]	[redacted] 01-Aug-2019 | 19:02 BST

US Sponsor: [redacted]	[redacted] 01-Aug-2019 | 10:01 PDT
Approved By: [redacted]	[redacted] 30-Jul-2019 | 04:04 PDT
Approved By: [redacted]	[redacted] 31-Jul-2019 | 04:01 PDT
Approved By: [redacted]	[redacted] 30-Jul-2019 | 04:09 PDT

INVESTIGATOR'S PROTOCOL REVIEW STATEMENT

By my signature, I confirm that my staff and I have carefully read and understand the protocol, A Phase III Clinical Trial of Intra-arterial TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (HCC), and agree to conduct the trial in accordance with the protocol, the appropriate regulations specified in the protocol, and the stipulations of the clinical study agreement

_____ _____

Investigator Date

_____ _____

Investigator Printed Name

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1.0 PROTOCOL SYNOPSIS

Protocol Number	TS-103
Protocol Short Title	STOP-HCC
Protocol Title	A Phase III Clinical Trial of Intra-arterial TheraSphere in the Treatment of Patients with Unresectable Hepatocellular Carcinoma (HCC)
Device	TheraSphere, Yttrium-90 glass microspheres In the European Union, TheraSphere has been CE marked for the treatment of hepatic neoplasia. TheraSphere is currently approved in Canada for treatment of hepatic neoplasia in patients who have appropriately positioned arterial catheters. TheraSphere is currently approved for commercial distribution in the United States under a Humanitarian Device Exemption (HDE) for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis/occlusion, when clinical evaluation warrants the treatment.
Standard-of-care Systemic therapy	Sorafenib
Type of Protocol	Phase III
Protocol Design	This is an open-label, prospective, multi-center, randomized clinical trial.
Study Objective	To evaluate TheraSphere in the treatment of patients with unresectable hepatocellular carcinoma in whom treatment with standard-of-care sorafenib therapy is planned.
Primary Endpoint	Overall Survival (OS) from time of randomization
Secondary Endpoints	• Time to progression (TTP) from time of randomization based on investigator assessment according RECIST criteria v 1.1 • Time to untreatable progression (TTUP) from the time of randomization based one or more of the following: investigator assessment according to RECIST criteria v 1.1, contraindication to protocol treatments based on package insert or patient performance status. • Time to symptomatic progression (TTSP) from the time of randomization to ECOG performance status > 1 with or without tumor progression based on investigator assessment according to RECIST criteria v 1.1. Deterioration in performance status is to be confirmed at two subsequent evaluations at 8 week intervals. • Tumor response according to RECIST v 1.1 criteria based on investigator assessment. Tumor response rate, according to the mRECIST criteria[20] and based on a blinded centralized independent imaging assessment, will be an exploratory endpoint. • Quality of life Assessments (including the Functional Assessment of Cancer Therapy – Hepatobiliary Questionnaire – FACT-Hep)

	• Adverse events (NCI-CTAE v 4.0)
[redacted]	• [redacted]
Trial Population	Patients diagnosed with unresectable HCC who are not eligible for any curative procedures and for whom standard-of-care therapy with sorafenib is planned.
Number of patients	The randomization of approximately 520 patients is planned, with up to a maximum of 700 patients being randomized based on a sample size re-estimation after the second interim analysis.
Number of sites	Up to 105 sites in North America, Europe and Asia
Treatment Groups	• The Control group will receive planned standard-of-care therapy sorafenib in accordance with the approved product labeling. • The Treatment group will receive TheraSphere prior to the initiation of standard-of-care sorafenib treatment. All liver tumors observed at baseline that are amenable to treatment with TheraSphere should be treated with TheraSphere prior to the initiation of treatment with sorafenib.
Study Duration	Approximately 60 months of accrual and 18 months additional follow-up is planned; with approximately 66 months of accrual if required following sample size re-estimation.

Eligibility Criteria	1. Must have signed informed consent prior to any study-related evaluation. 2. Must be male or female patients over 18 years of age 3. Must have unresectable HCC confirmed by histology or by non-invasive AASLD criteria 4. Must have measurable disease defined as at least one uni-dimensional measurable lesion by CT or MRI (according to RECIST 1.1) 5. Must have a Child Pugh score $\leq$ 7 points 6. Must have an ECOG Performance Status score of ≤ 1 7. Must have a life expectancy of 12 weeks or more 8. Must be eligible to receive standard-of-care sorafenib 9. Must have a Platelet count > 50 x 10^9/L or > 50% prothrombin activity 10. Must have a Hemoglobin ≥ 8.5 g/dL 11. Must have Bilirubin ≤ 2.5 mg/dL 12. ALT and AST must be < 5X upper limit of normal 13. Amylase or lipase must be ≤ 2X upper limit of normal 14. Serum creatinine must be ≤ 1.5X upper limit of normal 15. INR must be < 2.0 16. Must not have main portal vein thrombosis (PVT) (branch portal vein thrombosis is permissible). 17. Must not be eligible for curative treatment (e.g ablation or transplantation) 18. Must not have history of previous or concurrent cancer other than HCC unless treated curatively 5 or more years prior to entry 19. Must not have confirmed presence of extra-hepatic disease except lung nodules and mesenteric or portal lymph nodes ≤ 2.0 cm each 20. Must not be at risk of hepatic or renal failure 21. Must not have tumor replacement >70% of total liver volume based on visual estimation by the investigator OR must not have tumor replacement >50% of total liver volume in the presence of albumin <3 g/dL 22. Must not have any history of severe allergy or intolerance to contrast agents, narcotics sedatives or atropine that cannot be managed medically 23. Must not have any contraindications to angiography and selective visceral catheterization 24. Must not have history of organ allograft 25. Must not have any known contraindications to sorafenib including allergic reaction, pill-swallowing difficulty, evidence of severe or uncontrolled systemic diseases, uncontrolled severe hypertension or cardiac arrhythmias, congestive heart failure >New York Heart Association (NYHA) class 2, myocardial infarct within 6 months, prolonged QT/QTc >450ms, evidence of torsades de pointe, or laboratory finding that in the view of the investigator makes it undesirable for the patient to participate in the trial , significant GI bleed within 30 days,

	metastatic brain disease, renal failure requiring dialysis. 26. Must not be taking any of the following: Rifampicin, St. John's Wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone 27. Must not be taking any other systemic anticancer agent (e.g. docetaxel, doxorubicin, irinotecan etc.) 28. Must not be taking any substrate agents for CYP2B6 (buproprion, cyclophosphamide, efavirenz, ifosfamide, methadone, pacilitaxel, amodiaquine, repaglinide) 29. Must not be taking any UGT 1A1 and UGT 1A9 substrates (e.g., irinotecan) 30. Must not be taking P-Gp substrates (e.g., Digoxin) 31. Any prior liver resection must have taken place > 2 months prior to randomization 32. Treatment with other locoregional therapies (other than study treatment) has not been planned for the duration of the clinical study period 33. Has not received any prior external beam radiation treatment to the chest, liver or abdomen 34. Has not received any prior yttrium-90 microsphere treatment to the liver *35.* Prior treatment with transarterial chemoembolization (TACE) or bland embolization must have occurred > 2 months prior to randomization and must have been applied to a treatment field and/or lobe that is not to be treated under this protocol. For patients with tumor progression in the treatment field and/or lobe previously treated with TA(C)E, vessels feeding the tumor(s) must be assessed for adequate blood flow using angiography (cone beam computerized tomography (CBCT) strongly recommended), and the TACE or bland embolization must have been applied >6 months prior to randomization. 36. Has not received any anti-cancer therapy or any treatment with an investigational agent within 30 days prior to randomization 37. Must not have any adverse effect due to prior therapy that is unresolved at randomization 38. Has not received any prior systemic therapy for the treatment of HCC, including sorafenib given for more than 4 weeks during the 2 previous months prior to randomization; no prior sorafenib related toxicity 39. No evidence of pulmonary insufficiency or inadequately treated moderate grade or severe/very severe grade chronic obstructive pulmonary disease. 40. Must not have undergone any intervention for, or compromise of, the Ampulla of Vater 41. Must not have any clinically evident ascites (trace ascites on imaging is acceptable) 42. Must not be pregnant or breast-feeding 43. Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to randomization 44. Must not have any disease or condition that would preclude the safe use of TheraSphere, including concurrent dialysis treatment, or unresolved serious

	infections. Patients infected with HIV can be considered, however, they must be well-managed and well controlled with an undetectable viral load 45. Must not be participating in concurrent clinical trials evaluating treatment intervention(s).

Imaging Requirements	• Triple Phase CT – To determine liver volume measurement, identify hepatic vascular anatomy to determine TheraSphere dosimetry • Spiral CT abdomen/pelvis –performed with cuts of 10 mm or less in slice thickness contiguously in the axial plane to assess hepatic and extra-hepatic lesions according to the RECIST criteria v1.1. • Spiral CT Chest –performed with cuts of 10 mm or less in slice thickness contiguously in the axial plane to assess extra-hepatic lesions according to the RECIST criteria v 1.1 • MRI can replace CT scans; however, the same imaging modality should be used for all images in an individual patient throughout the study • Images for efficacy assessments will require a duplicate set of images in DICOM format Hepatic angiography and ^{99m}Tc-MAA– selective celiac and superior mesenteric arteriograms are needed to evaluate the hepatic arterial anatomy for the whole liver, as well as evaluation of potential sources of extra-hepatic blood supply to tumors. Repeat ^{99m}Tc-MAA may be needed to estimate cumulative lung shunt or re-asses GI flow.
Statistical Plan and Sample Size Calculation	This study is an adaptive trial using a group sequential design with overall survival (OS) as the primary efficacy endpoint. A modified Intention To Treat (mITT) Population will be used to analyze all efficacy endpoints. This population is defined as randomized patients who met the study eligibility criteria at randomization. The study is designed to detect a 3.5 month increase in median OS time, from 10.7 months in the sorafenib arm to 14.2 months in the TheraSphere arm (ie, hazard ratio = 0.754), using a log rank test. Due to uncertainty in the expected treatment effect, a sample size re-estimation is planned, which would allow the sample size to increase in order to detect a 3.0 month increase in median OS time, from 10.7 months in the sorafenib arm to 13.7 months in the TheraSphere arm (ie, hazard ratio = 0.781). A maximum of 417 deaths will yield 80% power to detect the target difference in median OS (ie, hazard ratio = 0.754) with a two-sided alpha of 0.05 using a group sequential design with 2 interim analyses. It is estimated that a maximum of 520 patients will need to be recruited over 60 months, with an 18 month additional follow-up period. This includes an adjustment to take account of an assumed 5% of patients who will be lost to follow-up and for whom a date of death is not recorded, and an assumed additional 5% of patients who will be erroneously randomized because they did not meet the eligibility criteria at randomization. [redacted] Analysis of primary endpoint OS will be compared between treatment arms using a log-rank test. The hazard ratio and corresponding two-sided 95% confidence interval (CI) for the treatment effect will be computed. Kaplan-Meier curves will also be produced. Interim analyses of primary endpoint: The first interim analysis is planned at approximately, but no less than, 188 deaths, with a two-sided p-value ≤0.0151

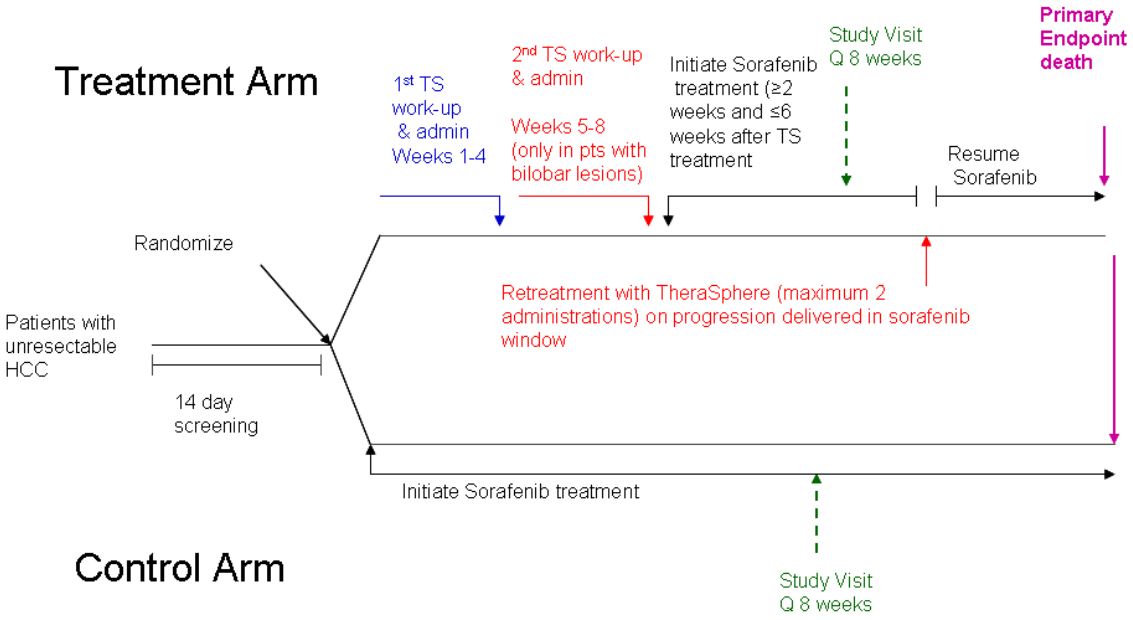
	allowing the study to be stopped early for efficacy. A second interim analysis is planned at approximately, but no less than, 250 deaths, with a two-sided p-value ≤0.0151 allowing the study to be stopped early for efficacy. A conditional power of less than or equal to 15% at each of the interim analyses will result in the study stopping early for futility. Sample size modification will be considered at the second interim analysis following the approach described in Mehta & Pocock (2011)[16] which employs an un-weighted test statistic at the final analysis as recommended by Burman & Sonneson (2006)[17]. Final Analysis of primary endpoint: The final analysis, without a sample size modification, will be performed when approximately, but no less than, 417 deaths have occurred. A two-sided p-value ≤0.0363 is required to declare a statistically significant improvement in median OS at the final analysis. If the sample size is increased after the second interim analysis, the final analysis will be performed when approximately, but no less than, 564 deaths have occurred, which will result in 80% power to detect an improvement in median OS from 10.7 to 13.7 months using a log rank test with a final two-sided alpha of 0.0363. Analysis of secondary efficacy endpoints Comparison between treatment groups for all secondary endpoints will be conducted at the final analysis with a two-sided alpha of 0.05. Time to event endpoints (ie, TTP, TTUP, TTSP) will be compared between treatment arms using a log-rank test. Tumor response rates will be compared between treatment arms using the continuity adjusted Newcombe-Wilson test. The FACT-Hep score will be compared between treatment arms using a mixed linear model with baseline score and the relative time from baseline as covariates. Safety Analysis: All patients who received study treatments at least once will be included in the safety analysis. All Adverse events (AEs) will be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) grades and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment emergent adverse events (events which were not present at baseline or worsened in severity following the start of treatment) will be summarized according to MedDRA primary system-organ class (SOC) and preferred term (PT). Laboratory values will be summarized by treatment group over time and overall. A feasibility safety assessment will be conducted after the first 20 patients in the treatment group have received both TS and sorafenib therapy. Poolability and Other Analysis: Multivariate Cox regression analysis of time-to-event efficacy endpoints will be conducted on stratification criteria and other factors such as age, gender, duration of disease prior to randomization. As a sensitivity analysis, to address the poolability of data across regions, study sites and gender, a Cox regression analysis of the primary efficacy endpoint, OS, will be conducted with factors of region, study site and gender, and to determine the impact of these factors on OS. Note: region and study site will not be included simultaneously in the model due to collinearity. Should the impact of region, site or gender on OS be statistically and clinically relevant, the reasons for the observed differential treatment effect, such as patient

	demographic or clinical characteristics, will be investigated and reported. If the poolability of OS results are in direct question as a result of this sensitivity analysis, the primary endpoint (OS) will also be analyzed separately by region, site or gender. In addition, the primary endpoint (OS) will be analyzed separately by US and non-US region. [redacted]
Screening Period	The following screening and enrollment evaluations should be performed within 14 days prior to randomization: • ICF (before any study required tests are performed), • Physical examination, • Medical history, • Child-Pugh assessment of chronic liver disease • Assessment of liver function, including presence/absence of portal hypertension and normal/abnormal bilirubin levels • ECOG Performance Status assessment • Triple-phase spiral CT/MRI to assess liver tumor presentation and estimate tumor burden in the liver. • Chest CT/MRI to rule out extra-hepatic metastases • FACT-Hep quality of life questionnaire • Required laboratory blood work plus α-feto protein (AFP) The date of screening is the date all screening procedures are completed
Randomization	Upon meeting eligibility for study participation in accordance with the Eligibility criteria, patients will be randomized 1:1 between the Treatment and Control groups

	In order to balance the treatment groups, patients will be stratified at randomization on the basis of Region (North America and Europe vs Asia), ECOG Performance Status (0 vs 1), presence or absence of branch portal vein thrombosis.
Control Group (Sorafenib)	All patients randomized to the Control group should start their planned standard-of-care treatment with sorafenib as soon as possible after randomization. Patients will follow standard dosing for sorafenib according to the product label information as prescribed by the investigator. Medically appropriate dose adjustments and drug holidays due to adverse events and toxicity are allowable.
Treatment Group (TheraSphere followed by Sorafenib)	As soon as possible after randomization, hepatic angiography will be performed to assess hepatic vascular anatomy and tumor hypervascularity, followed by a ^{99m}Tc-MAA scan to rule-out gastrointestinal flow or unacceptable lung shunting. Embolization may be performed, if necessary, to close off gastrointestinal flow so that the patient can qualify for treatment with TheraSphere. The lobe with the highest tumor burden should be scheduled for first treatment with TheraSphere. Patients will not be able to receive TheraSphere if the potential radiation dose to the lungs exceeds 30 Gy for a single treatment or cumulative 50 Gy or embolization cannot be performed to effectively block GI blood flow from the hepatic arterial system. If radiation exposure to the lungs exceeds 30 Gy (or 50 Gy cumulative), dose reduction of TheraSphere is permitted (minimum dose allowed is 90 Gy ± 10%). If after consideration of dose reduction, radiation exposure to the lung continues to be greater than 30 Gy (or 50 Gy cumulative), sorafenib treatment will be initiated as soon as possible and 99mTc-MAA will be repeated after 4 weeks of continuous treatment with sorafenib. If radiation exposure to the lung is less than 30Gy for a single treatment or 50Gy cumulative within a target dose of 90-120 Gy +10% , the patient may commence treatment with TheraSphere. In such instances, sorafenib should be discontinued at least 7 days prior to the administration of TheraSphere and resume sorafenib at least 2 weeks after the administration of TheraSphere. If radiation exposure to the lung is outside of the permitted range, treatment with sorafenib should be continued. In the case where TheraSphere could not be delivered at at target dose of 120 Gy ± 10% within 28 days of randomization, these patients will be included in the Treatment Group Intent-to-Treat analysis, but not in the Treatment Group Per-Protocol analysis. <u>TheraSphere Treatment #1</u>: TheraSphere treatment should occur within 28 days of randomization, and prior to the initiation of sorafenib. The number of infusions required to achieve lobar treatment will be determined by the Investigator, based on the hepatic vascular anatomy. Patients will receive 120 Gy ± 10% of TheraSphere to the treated lobe of the liver and may be administered in multiple infusions to address vascular abnormalities. <u>TheraSphere Treatment #2</u>: Patients who have bilobar disease at randomization should have TheraSphere administered to the untreated lobe. If needed, a second angiogram and/or ^{99m}Tc-MAA scan should be performed. Such treatments typically take place 28 days after the treatment to the first lobe. From 2 to 6 weeks following TheraSphere treatment of all treatable liver tumors observed at the time of randomization, patients should initiate standard-of-care sorafenib treatment in accordance with the sorafenib label directions. Re-treatment of the same patient with further cycles of TheraSphere is permitted if a

	treatable progression is detected during follow-up evaluations. Any re-treatment should take place a minimum of 28 days from the last TheraSphere treatment administered to that lobe. A maximum of 2 re-treatments are permitted in any patient.
Study Visits and Follow-up	Screening evaluations should be completed within 14 days prior to randomization. For patients randomized to sorafenib, study visits will take place every 8 weeks for as long as the patient remains on the trial. Additional visits may be scheduled as needed when initiating sorafenib treatment, and to manage any adverse events and adjustments to sorafenib dosing. For Patients randomized to TheraSphere, the pre-treatment evaluations and TheraSphere treatment to the first lobe should take place during the first 3 to 4 weeks following randomization. For patients with bilobar disease, the evaluations and TheraSphere treatment to the 2nd lobe should take place during weeks 5 to 8 weeks following randomization. After TheraSphere treatment, subsequent study visits will take place every 8 weeks from randomization for as long as the patient remains on the trial. After start of sorafenib therapy, patients may have additional visits as needed to adjust sorafenib dosing. Dosing of sorafenib should be consistent with the relevant label instructions, with allowance for appropriate adjustments based on the investigators medical judgment. In general, follow up visits take place approximately every 8 weeks from randomization until one of the study discontinuation criteria is met (see 9.2.19). The following assessments take place at the follow-up visit: o ECOG Performance Status assessment o Standard laboratory blood draw for CBC, differential, electrolytes, BUN, glucose, liver function test, coagulation panel, and α-fetoprotein biomarker o Triple phase spiral abdomen CT/MRI scan o Spiral CT/MRI scan of chest and pelvis o Child-Pugh Status o QOL questionnaire o Adverse event reporting Patients discontinuing sorafenib treatment in either arm of the study must be followed-up for survival until consent is explicitly withdrawn or any of the other study completion criteria is met (see Section 9.2.19).
Independent Data Monitoring Committee	This study will have oversight by an Independent Data Monitoring Committee who will meet as determined to review the enrollment, protocol deviations, and safety events. They will evaluate the data at interim analyses for consideration of stopping the study for overwhelming efficacy or futility and for sample size re-estimation at the second interim analysis. The IDMC will evaluate the final study report.
[redacted]	[redacted]

2.0 TRIAL SCHEMA



3.0 SCHEDULE OF EVENTS

Evaluation/Test Timing of Visit(s)	Screen Days -14 to 0	Rand-omize Day 0	Sorafenib for the Control Group Weeks 1-4 initiate Weeks 5 & thereafter continue therapy	1st TS work up & Adminis-tration Weeks 1-4	2nd TS work up & Adminis-tration Weeks 5-8	Sorafenib for the Treatment Group > 2 & < 6 weeks after TS – initiate & thereafter continue therapy	TS work up & re-treatment[1] After hepatic progression	Follow Up Until Death Q 8 weeks ± 14 days[8]	
								Prior to PD[9]	Post PD
Informed Consent	X								
Demographics	X								
Medical History	X								
Physical Exam (PE)	X								
ECOG Performance Status	X			X	X		X	X	
Medication & Prior Treatment History	X								
Review Eligibility Criteria	X								
Hematology: WBC, Hgb, Hct, Platelet	X		X[7]	X[7]			X	X	
Coagulation: PT, PTT, INR	X		X[7]	X[7]			X	X	
Chemistry panel, liver function tests	X		X[7]	X[7]			X	X	

Evaluation/Test Timing of Visit(s)	Screen Days -14 to 0	Rand-omize Day 0	Sorafenib for the Control Group Weeks 1-4 initiate Weeks 5 & thereafter continue therapy	1st TS work up & Adminis-tration Weeks 1-4	2nd TS work up & Adminis-tration Weeks 5-8	Sorafenib for the Treatment Group > 2 & < 6 weeks after TS – initiate & thereafter continue therapy	TS work up & re-treatment[1] After hepatic progression	Follow Up Until Death Q 8 weeks ± 14 days[8]	
								Prior to PD[9]	Post PD
Serum Pregnancy[2]	X						X		
Tumor makers for HCC (AFP)	X		X	X				X	
Liver Volume/Mass Calculation				X			X		
Randomize Patient		X							
Hepatic Angiogram, Tc-MAA[10] scan, TS Dose Calculation[3],				X	X		X		
Order TS[3]				X	X		X		
Administer TS[3 ,4, 10]				X	X		X		
Administer Sorafenib[5]			X			X	X[6]		
QOL questionnaire	X							X	
Triple Phase MRI/ Spiral CT ofabdomen	X							X	
Child-Pugh score	X							X	

Evaluation/Test **Timing of Visit(s)**	**Screen** **Days -14 to 0**	**Rand-omize** **Day 0**	**Sorafenib for the Control Group** **Weeks 1-4 initiate Weeks 5 & thereafter continue therapy**	**1st TS work up & Adminis-tration** **Weeks 1-4**	**2nd TS work up & Adminis-tration** **Weeks 5-8**	**Sorafenib for the Treatment Group** **> 2 & < 6 weeks after TS – initiate & thereafter continue therapy**	**TS work up & re-treatment[1]** **After hepatic progression**	**Follow Up Until Death** **Q 8 weeks ± 14 days[8]**	
								Prior to PD[9]	**Post PD**
Spiral CT of chest and pelvis	X							X	
Assess/Report Adverse Events	X		X	X	X		X	X	
Review/Record Concurrent Medication	X		X	X	X		X	X	
Final Endpoint Efficacy/Safety documentation & exit patient								X	X

[1] Additional TS work up & Administration in lesions amenable to further TS treatment[2] Female patients of childbearing potential only

[3] TS patients only

[4] Additional TS treatments may be administered only after progression if lesions are amenable to treatment

[5] According to package insert at Weeks 1-4 for Control group patients and after all initial TS administrations for Treatment group patients only

[6] Sorafenib to be stopped 7 days before subsequent TS administration on disease progression and restarted 2 weeks after TS is administered

[7] If treatment commences within 14 days of randomization the clinical laboratory assessments are not required to be repeated.

[8] The follow-up visits should be scheduled from the day of randomization. A window of ± 14 days is permissible from the scheduled date.

[9] Progression of disease resulting in termination of further treatment

[10] If available, ^{99m}Tc-MAA SPECT or SPECT-CT taken as part of the TS planning and post TS treatment imaging (Y-90 SPECT-CT or Y-90 PET-CT or Y-90 PET-MRI) taken as part of the TS administration quality control, will be collected retrospectively for exploratory analysis

4.0 LIST OF ABBREVIATIONS

AE - Adverse event

ADE – Adverse device effect

AFP – Alphafeto protein

ALT – Alanine Transaminase

AST – Aspartate Transaminase

BUN – Blood Urea Nitrogen

CBC – Complete Blood Count

CDR – Central Dosimetry Review

CRC – Colorectal Cancer

Cr - Chromium

CT – Computed Tomography

CTCAE – Common Toxicity Criteria for Adverse Events

DSMB – Data Safety Monitoring Board

ECOG – Eastern Cooperative Oncology Group

eCRF – electronic Case Report Form

FACT-Hep - Functional Assessment of Cancer Therapy – Hepatobiliary Questionnaire

FHSI8 – Functional Assessment of Cancer Therapy – Hepatobiliary Symptom Index 8

GBq - gigabecquerel

GI – gastrointestinal

Gy – Gray, a measure of irradiation dose

HCC – Hepatocellular Carcinoma

HDE – Humanitarian Device Exemption

ICF – Informed Consent Form

IDMC – Independent Data Monitoring Committee

INR – International Normalized Ratio for prothrombin time

IRB – Institutional Review Board

LFT – Liver function tests

MIRD - Medical Internal Radiation Dose

mITT – Modified Intention-To-Treat

NCI – National Cancer Institute

PE – Physical exam

PFS – Progression Free Survival

PT - Prothrombin Time

PTT – Partial Thromboplastin Time

RECIST – Response Evaluation Criteria in Solid Tumor

SAE – Serious adverse event

SADE – Serious adverse device effect

SOC – Standard-of-care

^{99m}Tc-MAA– Technetium-99m Magroaggregated albumin

TS - TheraSphere

TTP – Time-to-Progression

TTUP – Time-to-Untreatable Progression

UADE – Unanticipated Adverse Device Effect

WBC – White Blood Cells

Y-90 (Y-88, Y-91) – Ytrium-90 and isotopes

5.0 BACKGROUND AND RATIONALE

5.1 GENERAL DEVICE DESCRIPTION

TheraSphere® (TS) consists of insoluble glass microspheres in which yttrium-90 (Y-90) is an integral component of the glass. The sphere diameter ranges from 20 to 30 µm with 22,000 to 73,000 microspheres per milligram. TheraSphere is available in dose sizes ranging from 3 – 20 GBq (typically 3 GBq, 5 GBq, 7 GBq, 10 GBq, 15 GBq and 20 GBq) each supplied in 0.6 mL of sterile, pyrogen-free water contained in a 1.0 mL vial secured within a clear acrylic vial shield.

A pre-assembled single-use TheraSphere Administration Set is provided for each dose. Each user site is provided with a re-useable TheraSphere Administration Accessory Kit that provides both radiation protection for the user and physical support of the dose vial and Administration Set during administration of the product.

Yttrium-90 is a pure beta emitter which decays to stable zirconium-90 with a physical half-life of 64.2 hours. The average energy of the beta emissions from yttrium-90 is 0.9367 MeV with mean tissue penetration of approximately 2.5 mm.

TheraSphere is administered through the hepatic artery which supplies blood to tumor tissue (the portal vein supplies blood to the normal hepatic tissue). The microspheres are trapped in the vasculature of the tumor due to arteriolar capillary blockage where they exert a local radiotherapeutic effect. In clinical use, the glass microspheres remain permanently trapped in the vasculature where the isotope decays to infinity leaving background radiation with no therapeutic value.

5.2 GLOBAL REGULATORY STATUS OF THERASPHERE

TheraSphere received a Humanitarian Device Exemption (HDE) from the United States Food and Drug Administration (FDA) in 1999 (HDE H980006) and is currently approved for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis/occlusion, when clinical evaluation warrants the treatment. The current US package insert is provided in Appendix 1a.

TheraSphere is approved for use in Europe for the treatment of hepatic neoplasia. TheraSphere is approved in Canada for the treatment of hepatic neoplasia in patients who have appropriately positioned arterial catheters. In addition, TheraSphere is available commercially in Saudi Arabia, Hong Kong, Singapore, S. Korea, South Africa, Turkey, Kuwait, Brazil, Argentina and Mexico for the treatment of hepatic neoplasia. The current Canadian package insert and Instructions for Use in Europe are provided in Appendix 1b and 1c, respectively.

5.3 RATIONALE FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

According to the International Agency for Research on Cancer (IARC)[1], primary liver cancer is a major health problem worldwide. Globally, it is the sixth most commonly diagnosed cancer, with more than 749,000 new cases in 2011. It is the third leading cause of cancer death in men and sixth among women.

In North America and Western or Northern Europe, areas with historically low rates, the incidence of liver cancer is increasing, possibly due to increased prevalence of hepatitis C.

In 2007, the FDA[2] approved sorafenib tosylate (Nexavar®), a small molecule Raf kinase and VEGF receptor kinase inhibitor, for the treatment of patients with unresectable hepatocellular carcinoma (HCC).

The approval was based on the results of an international, multicenter, randomized, double-blind, placebo-controlled trial (SHARP[3] trial) in patients with unresectable, biopsy-proven hepatocellular carcinoma. Overall survival was the primary efficacy endpoint. A total of 602 patients were randomized; 299 to sorafenib 400 mg twice daily and 303 to matching placebo.

Demographics and baseline disease characteristics were similar between the sorafenib and placebo groups. Prior treatments included surgical resections (20 percent), locoregional therapies (including radiofrequency ablation, percutaneous ethanol injection and transarterial chemoembolization in 40 percent), radiotherapy (5 percent), and systemic therapy (4 percent).

The trial was stopped following a pre-specified second interim analysis for survival disclosing a statistically significant advantage for sorafenib [median 10.7 vs. 7.9 months; HR: 0.69 (95 percent CI: 0.55, 0.87), p= 0.00058]. The final analysis of time-to-tumor progression (TTP) by independent radiological review was based on data from an earlier time point and demonstrated a statistically significant improvement in TTP in the sorafenib group [median 5.5 vs. 2.8 months; HR: 0.58 (95 percent CI: 0.45, 0.74), p=0.000007].

Sorafenib is now suggested as the standard-of-care (SOC) therapy[4] for patients with advanced HCC, the patients classified as BCLC C according to the Barcelona Clinic Liver Cancer (BCLC) classification system. Sorafenib is included in the NCCN Clinical Practice Guidelines in Oncology[5] (NCCN– Hepatobiliary cancers V.1.2010 – HCC5) as one of the possible treatments for patients with unresectable HCC and extensive liver disease who are not candidates for transplantation.

Although sorafenib is a SOC in the treatment of patients with HCC, it is associated with only a modest improvement in median survival as compared to best supportive care. Further, sorafenib treatment is associated with significant toxicity. The most common adverse reactions[14] (≥20 percent) considered related to sorafenib were fatigue, weight loss, rash/ desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain. Diarrhea was reported in 55 percent of sorafenib patients (grade 3 in 10 percent). Hand-foot syndrome (21 percent overall; grade 3 in 8 percent) and rash (19 percent overall; grade 3 in 1 percent) were the most common dermatologic adverse reactions to sorafenib. Sorafenib dose reductions and drug holidays are often required to manage these toxicities.

Subsequent subset analysis of the SHARP trial data[6] indicated that the efficacy of sorafenib is reduced in an important subset of patients with advanced HCC. In patients with extrahepatic spread or macroscopic vascular invasion, the median survival was 8.9 months in patients treated with sorafenib as compared to 6.7 months in patients treated with placebo.

Salem et al[7] recently published their long-term experience of TheraSphere in the treatment of patients with HCC. In this report, patients with HCC (n=291) were treated with TheraSphere as part of a single-center, prospective, longitudinal cohort study. Toxicities were recorded using the Common Terminology Criteria version 3.0. Response rate and time to progression (TTP) were determined using World Health Organization (WHO) and European Association for the Study of the Liver (EASL) guidelines. Survival by stage was assessed. Univariate/multivariate analyses were performed. A total of 526 treatments were

administered (mean, 1.8; range, 1-5). Toxicities included fatigue (57%), pain (23%), and nausea/vomiting (20%); 19% exhibited grade 3/4 bilirubin toxicity. The 30-day mortality rate was 3%. Response rates were 42% and 57% based on WHO and EASL criteria, respectively. The overall median TTP was 7.9 months (95% confidence interval, 6-10.3). Median survival times differed between patients with Child-Pugh A and B disease (A, 17.2 months; B, 7.7 months; P = .002). Patients with Child-Pugh B disease who had portal vein thrombosis (PVT) had a median survival of 5.6 months (95% confidence interval, 4.5-6.7). Baseline age; gender; performance status; presence of portal hypertension; tumor distribution; levels of bilirubin, albumin, and alpha-fetoprotein; and WHO/EASL response rate predicted survival. These investigators concluded that patients with Child-Pugh A disease, with or without PVT, benefited most from treatment. Patients with Child-Pugh B disease who had PVT had poor outcomes. TTP and overall survival varied by patient stage at baseline.

Hilgard[8] et al report treatment of 108 consecutive patients with advanced HCC using TheraSphere. Median overall survival from day of treatment was 16.4 months for all patients, with median time to progression of 10.0 months. Tumor response at 90 days evaluated by RECIST in 62 patients were complete or partial response 10 (16%), stable disease 46 (74%) and progressive disease 6 (10%). Toxicities were generally mild to moderate with the most common being transient fatigue during the week following administration (61%) and abdominal pain (56%). One case of radiation cholecystitis was treated with cholecystemtomy. There was no Grade 3 or 4 lung toxicities. Lymphopenia was observed without clinical sequellae. Because hepatic decompensation is a known risk of yttrium-90 microsphere therapy, all elevations in bilirubin values were considered to be treatment related hepatotoxicties. For patients with normal bilirubin at enrollment, 32% experienced Grade 1 or 2 elevations and three patients developed Grade 3 elevations. For patients with elevated bilirubin at enrollment, 17% experienced Grade 2 elevations and 30% experienced Grade 3 or 4 elevations. In the majority of patients, bilirubin returned to baseline values within 4-6 weeks. The authors conclude the therapy is safe and effective, even in patients with compromised liver function.

At the International Liver Cancer Association conference in September 2010, Metrakos[9] et al reported preliminary results of a Phase II investigation of the safety, tolerability and efficacy of administering TheraSphere and Nexavar (sorafenib) treatment in patients with HCC. In this trial, all patients (N=26) began sorafenib 400 mg BID at least 7 weeks in advance of TheraSphere treatment which was administered in a sorafenib window. Most patients (65%) required sorafenib dosage adjustment. The most common toxicities were diarrhea, fatigue and hand foot syndrome with most being self-limiting and responsive to dose adjustment. One single grade 4 toxicity of worsening cirrhosis was observed. Median survival is 15.5 months which exceeds that reported in the sorafenib or placebo arms of the SHARP study (10.7 and 7.9 months respectively). The reported toxicities are consistent with the toxicity profile of both TheraSphere and sorafenib with no apparent increase in severity or frequency.

As illustrated by these published reports, there is now an extensive clinical experience demonstrating the safety of TheraSphere in the management of patients with unresectable HCC.

The early reports of serious adverse events possibly associated with the use of TheraSphere included death, hepatorenal failure, liver abscess, hepatic encephalopathy, hepatic decompensation, radiation hepatitis, radiation pneumonitis, duodenal ulcer, gastrointestinal bleeding and cholecystitis. As clinical experience with TheraSphere increased, the pre-treatment high risk factors associated with these early serious events were identified, leading to improved patient selection criteria and thereby lowering the risk of these events occurring. These risk factors include infiltrative tumor type, bulk disease (tumor volume >70% or nodules

too numerous to count), AST or ALT > five times the upper limit of normal, bilirubin > 2 mg/dL, tumor volume >50% in the presence of an albumin < 3 g/dL and those in whom extra-hepatic shunting to the lungs or gastrointestinal tract cannot be managed through standard angiographic techniques.

For those patients without the pre-treatment high risk factors noted above, TheraSphere is very well tolerated, with treatment in the US commonly administered in an outpatient setting. Hospitalization for treatment effects associated with TheraSphere administration is rare. The most commonly reported adverse events associated with TheraSphere administration are fatigue, abdominal pain, nausea/vomiting and transient laboratory values including elevated bilirubin, AST, ALT, alkaline phosphatase, decreased platelets and lymphocyte depression with no clinical sequelae.

In this trial, all patients with unresectable HCC eligible for treatment with SOC sorafenib may be considered for study participation. Patients who meet the entry criteria will be randomized to either the patient's planned SOC sorafenib therapy (Control group), or to TheraSphere administered prior to the patient's SOC sorafenib therapy (Treatment group). The primary outcome measure for this trial is overall survival.

Our outcome assumption in the Control group is based on the SHARP trial, with a median overall survival of 10.7 months for patients treated with sorafenib. We assume a median overall survival of 14.2 months in the Treatment group, (hazard ratio = 0.754). However, due to uncertainty in the expected treatment effect, a sample size re-estimation is planned, which would allow the sample size to increase in order to detect a smaller increase in median OS time, from 10.7 months in the sorafenib arm to 13.7 months in the TheraSphere arm (ie, hazard ratio = 0.781).

[redacted]

6.0 STUDY OBJECTIVE

The objective of this clinical study is to evaluate TheraSphere in the treatment of patients with unresectable hepatocellular carcinoma.

7.0 STUDY DESIGN

This is an open-label prospective, multi-center, randomized clinical trial. Patients with unresectable hepatocellular carcinoma in whom SOC sorafenib therapy is planned are eligible to participate. The trial will evaluate the use of TheraSphere followed by the SOC sorafenib treatment. Up to 105 study centers will participate and recruit patients for the protocol. Participating study sites may be in the United States, Canada, Europe and Asia. All patients will be followed prospectively from randomization to death.

8.0 STUDY POPULATION AND ELIGIBILITY CRITERIA

Patients diagnosed with unresectable HCC who are not eligible for any curative procedures, and in whom treatment with SOC sorafenib is planned, may be screened for possible participation.

8.1 ELIGIBILITY CRITERIA

Patients must meet all eligibility criteria:

1. Must have signed informed consent prior to any study-related evaluation
2. Must be male or female patients over 18 years of age
3. Must have unresectable HCC confirmed by histology or by non-invasive AASLD[10] criteria
4. Must have measurable disease defined as at least one uni-dimensional measurable lesion by CT or MRI (according to RECIST 1.1)
5. Must have a Child Pugh score ≤ 7 points
6. Must have an ECOG Performance Status score of ≤ 1
7. Must have a Life expectancy of 12 weeks or more
8. Must have be eligible to receive SOC sorafenib
9. Must have Platelet count > 50 x 10^9/L or > 50% prothrombin activity
10. Must have Hemoglobin ≥ 8.5 g/dL
11. Must have Bilirubin ≤ 2.5 mg/dL
12. ALT and AST must be < 5X upper limit of normal
13. Amylase or lipase must be ≤ 2X upper limit of normal
14. Serum creatinine must be ≤ 1.5X upper limit of normal
15. INR must be ≤ 2.0
16. Must not have main PVT (branch portal vein thrombosis is permissible)
17. Must not be eligible for curative treatment (e.g ablation or transplantation)
18. Must not have a history of previous or concurrent cancer other than HCC unless treated curatively 5 or more years prior to entry
19. Must not have confirmed presence of extra-hepatic disease with the exception of lung nodules and mesenteric or portal lymph nodes ≤ 2.0 cm each
20. Must not be at risk of hepatic or renal failure

21. Must not have tumor replacement ≥70% of total liver volume based on visual estimation by the investigator OR must not have tumor replacement ≥50% of total liver volume in the presence of albumin <3 g/dL
22. Must not have any history of severe allergy or intolerance to contrast agents, narcotics sedatives or atropine that cannot be managed medically
23. Must not have any contraindications to angiography and selective visceral catheterization
24. Must not have history of organ allograft
25. Must not have any known contraindications to sorafenib including allergic reaction, pill-swallowing difficulty, evidence of severe or uncontrolled systemic diseases, uncontrolled severe hypertension or cardiac arrhythmias, congestive cardiac failure >New York Heart Association (NYHA) class 2, myocardial infarct within 6 months, prolonged QT/QTc >450ms, evidence of torsades de pointe, or laboratory finding that in the view of the investigator makes it undesirable for the patient to participate in the trial , significant GI bleed within 30 days, metastatic brain disease, renal failure requiring dialysis.
26. Must not be taking any of the following: Rifampicin, St. John's Wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone
27. Must not be taking any other systemic anticancer agent (e.g docetaxel, doxorubicin, irinotecan etc.)
28. Must not be taking substrate agents for CYP2B6 (buproprion, cyclophosphamide, efavirenz, ifosfamide, methadone, pacilitaxel, amodiaquine, repaglinide)
29. Must not be taking UGT 1A1 and UGT 1A9 substrates (e.g., irinotecan)
30. Must not be taking P-Gp substrates (e.g., Digoxin)
31. Any prior liver resection must have taken place ≥ 2 months prior to randomization
32. Treatment with other locoregional therapies (other than study treatment) has not been planned for the duration of the clinical study period
33. Has not received any prior external beam radiation treatment to the chest, liver or abdomen
34. Has not received any prior yttrium-90 microsphere treatment to the liver
35. Prior treatment with transarterial chemoembolization (TACE) or bland embolization must have occurred > 2 months prior to randomization and must have been applied to a treatment field and/or lobe that is not to be treated under this protocol. For patients with tumor progression in the treatment field and/or lobe previously treated with TA(C)E, vessels feeding the tumor(s) must be assessed for adequate blood flow using angiography (cone beam computerized tomography (CBCT) strongly recommended), and the TACE or bland embolization must have been applied >6 months prior to randomization.
36. Has not received any anti-cancer therapy or any treatment with an investigational agent within 30 days prior to randomization
37. Must not have any adverse effect due to prior therapy that is unresolved at randomization
38. Has not received any prior systemic therapy for the treatment of HCC, including sorafenib given for more than 4 weeks during the 2 previous months prior to randomization; no prior sorafenib related toxicity
39. No evidence of pulmonary insufficiency or inadequately treated moderate grade or severe/very severe grade chronic obstructive pulmonary disease
40. Must not have undergone any intervention for, or compromise of, the Ampulla of Vater

41. Must not have any clinically evident ascites (trace ascites on imaging is acceptable)
42. Must not be pregnant or breast-feeding
43. Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to randomization
44. Must not have any disease or condition that would preclude the safe use of TheraSphere, including concurrent dialysis treatment, or unresolved serious infections. Patients infected with HIV can be considered, however, they must be well-managed and well controlled with an undetectable viral load
45. Must not be participating in concurrent clinical trials evaluating treatment intervention(s).

9.0 STUDY VISITS, EVALUATIONS AND PROCEDURES

9.1 STUDY VISITS

Study treatment visits should occur at the time intervals outlined below and in the study visit schedule in Section 3.0. All study visits that take place after the screening/randomization period should occur within +/- 14 days of the designated time interval for that study visit.

9.1.1 SCREENING/RANDOMIZATION (DAYS -14 TO DAY 0)

All screening and baseline evaluations must be completed within 14 days prior to randomization. CT/MRI scans obtained for clinical management within 28 days prior to randomization may be used for screening and baseline evaluations, as long as these scans conform to the protocol image specifications for efficacy and RECIST 1.1. Results from SOC tests and examinations taken within 14 days prior to randomization may be used.

The following activities will be completed during the screening period within 14 days prior to randomization.

1. Informed Consent must be signed (as described in Section 13.7.
2. Patient demographic information will be collected as described in Section 9.2.2.
3. Medical History information will be collected as described in Section 9.2.3.
4. A physical examination as described in Section 9.2.4 will be done.
5. ECOG Performance Status will be assessed as described in Section 9.2.5.
6. Medication history & Prior treatment history will be obtained as described in Section 9.2.7.
7. The liver tumor volume calculation will be completed as described in Section 9.2.8.
8. Baseline clinical laboratory tests, blood chemistry, hematology and coagulation, as described in Section 0 will be done.
9. Child-Pugh assessment of chronic liver disease
10. A serum pregnancy test as described in Section 9.2.10 will be administered for all female patients of childbearing potential.
11. The patient's eligibility to participate will be assessed as described in Section 9.2.11.
12. A baseline AFP level will be drawn.
13. Baseline images for efficacy evaluation (Spiral CT of abdomen/pelvis and Spiral CT of chest) will be taken as described in Section 9.2.16.
14. Baseline Quality of Life assessments will be made as described in Section 9.2.13.

Following Screening, patients meeting the eligibility criteria will be randomized as described in Section 9.2.14.

The date of screening is the date all screening procedures are completed

9.1.2 Patients randomized to the Control Group

9.1.2.1 Weeks 1-4 following Randomization – Control Group

The following clinical patient management activities will be completed as appropriate and documented on the electronic case report forms. Patients may need several visits during this period to adjust the dose of sorafenib.

1. If treatment with sorafenib commences greater than 14 days after randomization, , complete appropriate clinical laboratory tests, including AFP, prior to treatment as described in Section 0.
2. Administer SOC sorafenib in Control Group as described in Section 9.2.15.2.
3. Record details on the clinical assessments and administration of sorafenib.
4. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.2.

9.1.2.2 Q 8 Weeks Following Randomization – Control Group

In addition to the administration of sorafenib and the evaluations associated with that therapy, at every 8 week visit following randomization, the following will be completed:

1. Clinical laboratory tests as described in Section 0.
2. CT/MR images will be taken as described in Section 9.2.16 for efficacy assessment.
3. Quality of Life assessments will be obtained as described in Section 9.2.13.
4. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.2.

For patients who discontinue sorafenib due to progressive disease and are unable to come in to the clinic for routine visits, sites should maintain telephone contact until death.

9.1.3 Patients randomized to the Treatment Group

9.1.3.1 Weeks 1-4 following Randomization – Treatment Group

The following clinical patient management activities will be completed and documented on the electronic case report forms (eCRF):

1. If treatment commences greater than 14 days after randomization , complete appropriate clinical laboratory tests, including AFP, prior to treatment, as described in Section 0.
2. Conduct TheraSphere pre-treatment evaluations and administer TheraSphere in Treatment Group as described in Section 9.2.15.1.
3. Record details on the clinical assessments and administration of TheraSphere
4. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.2.

9.1.3.2 Weeks 5-8 following Randomization – Treatment Group

The following clinical patient management activities will take place and will be documented on the eCRF:

1. Complete appropriate clinical laboratory tests as described in Section 0.

2. Administer TheraSphere as described in Section 9.2.15.1.6 to the second lobe for patients in the Treatment Group with a bilobar treatment plan.
3. Record details on the clinical assessments and administration of TheraSphere
4. Record any treatments and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.2.

9.1.3.3 >2 & <6 Weeks after complete TheraSphere Treatment

The following clinical patient management activities will take place and will be documented on the eCRF:

1. Administer SOC sorafenib in Treatment Group as described in Section 9.2.15.2.
2. Record details on the clinical assessments and administration of sorafenib.
3. Record any concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.2.

9.1.3.4 TheraSphere Re-treatment after Hepatic Progression – Treatment Group

Additional TheraSphere treatments may be administered after hepatic progression if the lesions are amenable to treatment. The following activities will take place:

1. Complete appropriate clinical laboratory tests, as described in Section 0.
2. Conduct TheraSphere pre-treatment evaluations and administer TheraSphere in Treatment Group as described in Section 9.2.15.1.
3. Record details on the clinical assessments and administration of TheraSphere
4. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.2.

9.1.3.5 Q 8 Weeks Following Randomization – Treatment Group

In addition to the administration of SOC sorafenib and the evaluations associated with that therapy, at every 8 week visit following randomization, the following will be completed:

1. Clinical laboratory tests as described in Section 0.
2. CT/MR images will be taken (as described in Section 9.2.16) for efficacy assessment.
3. Quality of Life assessments will be obtained as described in Section 9.2.13.
4. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.2.

For patients who discontinue study treatment due to progressive disease and are unable to come in to the clinic for routine visits, sites should maintain telephone contact until death.

9.1.4 Patient Completion or Early Withdrawal

If a patient completes the trial or withdraws early, the following activities will be completed as appropriate:

1. Record the date and reason for study exit, as described in section 9.2.19
2. Record the ECOG status as described in Section 9.2.5, as appropriate
3. Complete, as appropriate, any clinical laboratory tests, including AFP, as described in Section 0
4. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.2
5. Complete any CT/MR images, as appropriate, for efficacy assessment.
6. Complete the Quality of Life assessments, as appropriate, as described in Section 9.2.13.

9.2 STUDY EVALUATIONS AND PROCEDURES

9.2.1 POTENTIALLY ELIGIBLE PATIENTS AND INFORMED CONSENT

Any patient who appears to meet the eligibility criteria may be offered the opportunity to be evaluated for participation in this clinical trial. All such patients must sign an IRB approved informed consent form, and have the opportunity to ask the Investigator any questions regarding the trial, and their rights and obligations as a trial participant before any protocol related evaluations can be performed. The details regarding informed consent are described in Section 13.7.

9.2.2 DEMOGRAPHICS

Demographic data (age, gender, female childbearing potential, race, and ethnicity) will be obtained.

9.2.3 MEDICAL HISTORY

Medical history deemed clinically significant by the Investigator will be collected per body system (allergy/immunology, auditory/ear, blood/bone marrow, cardiac arrhythmia, cardiac general, dermatology/skin, endocrine metabolic, gastrointestinal, hemorrhage/bleeding, Hepatobiliary/pancreatic, infection, musculoskeletal/soft tissue, neurologic, ocular/vision, psychiatric, pulmonary/upper respiratory, renal/genitourinary, sexual reproductive function, vascular).

The diagnoses and history of HCC will be recorded separately from other medical history and will include assessment of liver function, including Child-Pugh assessment of chronic liver disease, and presence of portal hypertension.

All on-going medical conditions and adverse events arising from treatment of those conditions present for ≥ 30 days are generally considered a part of the patient's medical history and must be recorded at baseline.

9.2.4 PHYSICAL EXAMINATION

A physical examination will also be performed, which will cover the following:

- Vital signs: heart rate (HR), respiratory rate (RR), blood pressure (BP) taken after sitting for 5 minutes, and temperature (T)
- Height and weight
- Head, eyes, ears, nose, and throat
- Chest
- Heart
- Abdomen
- Extremities
- Brief neurological examination (level of consciousness, orientation, sensation, and motor function)
- Genitourinary, endocrine and allergy/immunology systems

9.2.5 ECOG PERFORMANCE STATUS

ECOG Performance Status[11] will be assessed according to the following categories:

Score	Characteristics
0	Asymptomatic and fully active

1	Symptomatic; fully ambulatory; restricted in physically strenuous activity
2	Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed.
3	Symptomatic; limited self-care; more than 50% of waking hours are spent in bed
4	Completely disabled; no self-care; bedridden.

9.2.6 CHILD-PUGH SCORE STATUS

Severity of liver disease will be assessed according to the Child-Pugh classification of Severity of Liver Disease (see Appendix 4) at screening and at every 8 weeks visit.

9.2.7 MEDICATION AND PRIOR TREATMENT HISTORY

The use of prior and concurrent medications (medications taken within 30 days of screening and during the conduct of the study respectively) will be obtained and documented on the relevant eCRF. Palliative medications and/or HCC treatments administered for patients discontinuing sorafenib must also be documented.

Prior treatments for HCC will be recorded separately from treatment for other medical conditions.

The start and stop dates for all such prior treatments for HCC or other cancer treatments as well as prior treatment of other medical conditions should be recorded.

9.2.8 LIVER TUMOR VOLUME DETERMINATION

Triple Phase CT is the fastest and most reproducible method of capturing liver volume measurement and mass calculations required prior to TheraSphere treatment. Accurate imaging and volume calculation are essential for calculation of TheraSphere dosimetry.

Using institutional standard equipment and techniques, lobar and tumor regions of interest will be drawn and the respective lobar and tumor volumes determined (a detailed discussion begins on page 1259 in Appendix 2).

Tumor replacement, expressed as a per cent of total liver volume, will be recorded on the relevant eCRF.

9.2.9 CLINICAL LABS

The following clinical laboratory assessments will be completed at study visits during the trial and must be documented as described in Section 13.4. Laboratory assessments undertaken as part of SOC clinical assessment may be used.

- Hematology: complete blood cell count (cBC) , differential white blood count (WBC), platelet count, hematocrit, hemoglobin,
- Coagulation: Prothrombin Time (PT), Partial Thromboplastin Time (PTT), International Normalized ratio for prothrombin time (INR)
- Chemistry panel: serum creatinine, blood urea nitrogen (BUN), glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, amylase, lipase, total bilirubin, and alkaline phosphatase.

- Alpha-fetoprotein (AFP)

9.2.10 PREGNANCY TEST

A serum pregnancy test for females of child-bearing potential will be performed at the screening visit. Patients determined to be pregnant are not eligible to participate in this clinical trial.

Female patients of childbearing potential must be advised that they should not become pregnant while participating in this clinical trial. Adequate methods of contraception must be used by these patients while they are enrolled in this clinical trial. Patients should not be breastfeeding while participating on this trial.

9.2.11 REVIEW ELIGIBILITY CRITERIA

Data detailing Demographic, Medical History, Physical Examination, ECOG Performance Status, Medication and Prior Oncologic Treatment, Tumor volume and Clinical Labs will be reviewed against eligibility criteria to determine eligibility. The determination will be recorded on the relevant case report form (eCRF).

9.2.12 HCC TUMOR BIOMARKER

Blood will be collected prior to and at the 8 weeks study visits following randomization to determine the baseline and subsequent AFP values.

9.2.13 QUALITY OF LIFE

Functional Assessment of cancer Therapy – Hepatobiliary Questionnaire (FACT-HEP) quality of life instruments suitable for patients being treated for hepatocellular carcinoma will be administered at study visits every 8 weeks throughout the trial until death. The baseline QOL assessment will be obtained after the Informed Consent is signed and before the first treatment in either group is administered.

9.2.14 RANDOMIZATION (STUDY DAY 0)

Patients will be randomized 1:1 to study treatment, either the Control group or the Treatment group.

If a patient is determined to be eligible to participate in the trial, the study site will contact the central randomization office where randomization will be determined using assignment by a computer-generated randomization scheme. Upon randomization, each patient will be assigned a subject identity code consisting of the protocol number, the country code (e.g.01), the site number (e.g. 01) and a patient number (e.g. 001).

In order to create a balance between study groups, patients will be stratified at randomization based on the following:

- Region (North America and Europe versus Asia)
- ECOG performance status (0 vs 1)
- Presence or absence of branch portal vein thrombosis

Patients randomized to the Control group or the Treatment group who are unable to receive their planned study treatment will continue to be followed under their assigned study group for the purpose of the intent-to-treat analysis.

If a patient is found ineligible for the study, the patient will not be randomized and the reason for treatment ineligibility should be documented on the Screen Failure Log.

9.2.15 STUDY TREATMENTS

9.2.15.1 THERASPHERE

TheraSphere will be administered to the diseased lobes present at randomization, before initiation of the SOC sorafenib treatment. Patients with unilobar disease will receive treatment of the diseased lobe. Patients with bilobar disease will have the second procedure visit such that the second administration occurs within Weeks 5-8 following randomization.

SOC Sorafenib will be prescribed in accordance with the sorafenib package insert. To minimize the risk of additive or synergistic adverse events, sorafenib and TheraSphere should not be administered concurrently. SOC sorafenib treatment will be initiated at least two (2) weeks after the administration of TheraSphere is completed. Generally, patients should initiate SOC sorafenib between 2 and 6 weeks after TheraSphere has been administered to all disease present at randomization.

Safety Risks will be minimized by treating all liver tumors present at randomization with TheraSphere followed by an interval of at least 2 weeks prior to initiating sorafenib therapy to allow decay of the radioactive microspheres and recovery from the expected transient adverse effects (fatigue, abdominal pain, nausea/vomiting) associated with TheraSphere administration. Ideally, SOC sorafenib should be started no later than 6 weeks following TheraSphere treatment.

During follow-up, for patients in the Treatment group who have demonstrated hepatic progression with hepatic lesions amenable to TheraSphere, re-treatment with TheraSphere is allowed. Sorafenib will be discontinued seven (7) days prior to TheraSphere treatment (equivalent to approximately five to seven half-lives) through 2 weeks after TheraSphere treatment to permit radioactive decay and patient recovery from transient side effects.

9.2.15.1.1 THERASPHERE PRE-TREATMENT EVALUATION

Patients randomized to the Treatment group must undergo the following evaluations to determine eligibility to receive the TheraSphere. These are described in detail in Appendix 2, pages 1254-1255 and include:

- Hepatic Angiography: selective celiac and superior mesenteric arteriograms are needed to evaluate the hepatic arterial anatomy for the whole liver, as well as evaluation of potential sources of extra-hepatic blood supply to tumors. The goal is to identify, within the hepatic vascular anatomy, a catheter placement location that allows a single TS infusion throughout the lobar tumor volume without administration of microspheres to extra-hepatic structures.

- A technetium-99m macroaggregated albumin (^{99m}Tc-MAA) scan is used to assess the potential for shunting microspheres to the lungs as well as the potential for the deposition of microspheres to the gastrointestinal (GI) tract. Repeat ^{99m}Tc-MAA may be needed for subsequent treatments to estimate cumulative lung shunt or re-asses GI flow. Note that 3 technical factors, as discussed in Appendix 2 (time between administration of ^{99m}Tc-MAA and the scan, ^{99m}Tc-MAA particle size and the presence of free ^{99m}Tc-MAA) can lead to an over-estimation of shunting to the lungs and should be controlled.

TheraSphere should not be administered to a patient randomized to the Treatment group if:

- Deposition of microspheres to the GI tract that cannot be corrected by placement of the catheter distal to collateral vessels or the application of standard angiographic techniques, such as coil embolization to prevent deposition of microspheres in the GI tract.

- Exposure of radiation to the lungs of 30 Gray (Gy) for a single infusion or a cumulative 50 Gy limit for all infusions of TheraSphere - estimated during TheraSphere dose calculation as described in Section 9.2.15.1.3

In the event that the patient is determined not to be suitable and/or cannot be safely treated with TheraSphere, that patient may proceed to treatment with the planned SOC sorafenib regimen as described in Section 9.2.15.2.

9.2.15.1.2 THERASPHERE ADMINISTRATION STRATEGY

For patients eligible to receive TheraSphere, the administration strategy (choice of artery position to infuse the target vascular bed; selection of placement of coil embolization or other techniques used to prevent microsphere deposition to the GI tract) should be determined as discussed in Appendix 2, pages 1254 - 1257. Dosimetry is based on the volume of the target vascular bed supplied by the artery selected for infusion. Patients requiring coil embolization to prevent microsphere disposition to the GI tract should undergo this procedure during TheraSphere work-up.

Since the treatment approach for TheraSphere is lobar, proper imaging and volume calculation is essential for dosimetry purposes. The ability to understand hepatic anatomy relies on the sound understanding of the Couinaud hepatic segments[12]. Anatomically, the middle hepatic vein separates the right and left lobes. When drawing regions of interest and calculating lobar volumes, it is the middle hepatic vein that should be used as the anatomic delineator between the right and left lobes. If the middle hepatic vein cannot be seen, then the gallbladder and its axis relative to the liver can be used. This technique assumes

standard arterial anatomy with single right and left hepatic arteries. If variants are observed angiographically, for example, an accessory right hepatic artery, then accurate angiographic correlations must be performed when drawing the regions of interest for lobar or segmental lobar volumes. This will ensure that accurate volumes are obtained and three or more infusions are administered. The volume that needs to be used for Y-90 dosimetry is that volume of liver that is perfused by the vessel that will be infused. Target liver mass is determined by the positioning of the delivery catheter in the hepatic vasculature and the resulting liver area (segments) infused. Since there is considerable individual variation in hepatic vascular anatomy, the determination of target liver mass will depend on the variant encountered. The Table below presents the most commonly encountered variants with the corresponding segments associated to them.

STANDARD AND VARIANT HEPATIC VASCULAR ANATOMY AND CORRESPONDING COUINAUD SEGMENTS

Hepatic Vascular Anatomy[a]: Angiographic Findings	**Target Segments – Infusion 1[b]**	**Target Segments – Infusion 2**	**Target Segments – Additional Infusion**
Standard right and left hepatic arteries	1, 5, 6, 7, 8	2, 3, 4	
Replaced right hepatic with flow to medial segment left lobe	1, 4, 5, 6, 7, 8	2, 3	
Replaced right hepatic artery without flow to middle lobe, left hepatic artery with flow to medial and lateral segments left lobe	1, 5, 6, 7, 8	2, 3, 4	
Replaced left hepatic artery without flow to medial lobe	1, 4, 5, 6, 7, 8	2, 3	
Replaced left hepatic artery with flow to medial lobe	1, 5, 6, 7, 8	2, 3, 4	
Accessory right hepatic artery	6, 7	2, 3, 4	1, 5, 8
Right hepatic artery in the presence of an accessory right hepatic	5, 8	2, 3, 4	1, 6, 7
Middle hepatic artery (irrespective of origin)	1, 5 ,6, 7, 8	4	2, 3

Notes:
a) vascular anatomy subject to variation
b) assumes caudate lobe (segment 1) derives blood supply from right hepatic artery
c) caudate lobe (segment 1), right anterior lobe (segments 5/8), right posterior lobe (segments 6/7), left medial lobe (4), left lateral lobe (2, 3)

9.2.15.1.3 THERASPHERE DOSE DETERMINATION

The screening angiogram and ^{99m}Tc-MAA scan are used to determine lobar liver volume from CT or MR images, to identify vascular shunting to the gastrointestinal tract requiring use of angiographic occlusion techniques and to determine the lung shunt fraction. The target dose is 120 Gy ± 10%. If radiation exposure to the lungs exceeds 30 Gy (or 50 Gy cumulative), dose reduction of TheraSphere is permitted to a minimum dose of 90 Gy ± 10%.

If after consideration of dose reduction, radiation exposure to the lung continues to be greater than 30 Gy (or 50 Gy cumulative), sorafenib treatment will be initiated as soon as possible and 99mTc-MAA will be repeated after 4 weeks of continuous treatment with sorafenib. If radiation exposure to the lung is less than 30Gy for a single treatment (or 50 Gy cumulative) within a target dose of 90-120 Gy +10% , the patient may commence treatment with TheraSphere. In such instances, sorafenib should be discontinued

at least 7 days prior to the administration of TheraSphere and resume sorafenib at least 2 weeks after the administration of TheraSphere. If radiation exposure to the lung is outside of the permitted range, treatment with sorafenib should be continued. Calculation of Lung Shunt Factor: Lung shunt factor is determined from the ^{99m}Tc-MAA scan using the following equation: Lung shunt Fraction (F) = total lung counts/(total lung+ liver counts)

Calculation of Target Liver Mass (kg): Convert the target liver volume to mass assuming a conversion factor of 0.00103kg/cm^3.

Calculation of Activity required to deliver the desired dose of 120 Gy:
The amount of radioactivity required to deliver the desired target dose (120 Gy) to the selected liver target, adjusted for the estimated fraction that will be shunted to the lung, is calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}]\,[\text{Mass of Selected Liver Target (kg)}]}{50[1\text{-}F]}$$

Calculation of estimated lung radiation exposure (Gy):

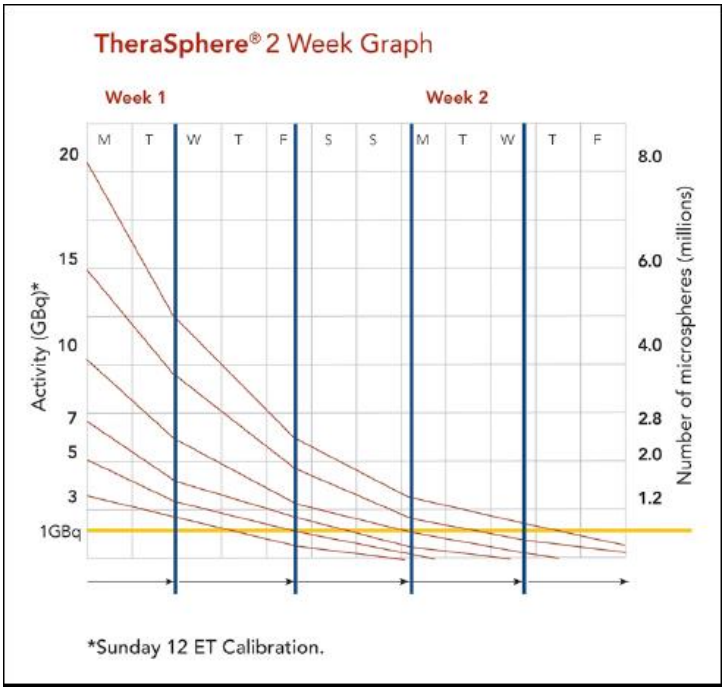
Lung Dose (Gy) per infusion = 50 * Calculated Activity in gigabecquerel (GBq) * F

Cumulative exposure is the sum of estimated exposure per infusion for all planned infusions.

9.2.15.1.4 THERASPHERE DOSE VIAL SELECTION

Selection of the dose vial size to supply the required activity (GBq) for delivery of the desired target dose to the selected target liver volume via the selected vascular route is dependent on the day and time of the scheduled patient treatment and must account for the time zone in which the hospital is located and the decay in radioactivity over time. The impact of time for available dose sizes is illustrated in the decay curve below.

The TheraSphere Treatment Window Illustrator can be used to select the appropriate dose vial or combination of dose vial(s) required to deliver the calculated activity required.



9.2.15.1.5 THERASPHERE ORDERING

Orders must be placed using the order form provided by the sponsor. Standard dose vial sizes (3 GBq, 5GBq, 7GBq, 10 GBq, 15GBq and 20GBq) are made to stock and can be ordered at anytime. Orders for custom size dose vials must be received at TheraSphere Customer Services by 12 noon Eastern Time on the Tuesday before the desired Calibration Date (approximately Day 7-10 post-randomization). TheraSphere will be delivered to the institution's designated radiopharmacy and handled according to institutional practices.

Each vial of TheraSphere will be shipped with a packing slip, a copy of which must be transferred to the study coordinator for device accountability so that the vials used can be tracked to the specific infusion(s) for each patient. Disposal of used or any unused vials will be handled in accordance with hospital standard practices for disposal of radioactive materials.

9.2.15.1.6 THERASPHERE ADMINISTRATION

TheraSphere will be administered at a dose of 120 ± 10% Gy to each lobe of the liver administered in one or more lobar administrations on separate days at least 28 days apart.

Patients in the Treatment group who have hepatic progression with hepatic lesions that are still amenable to TheraSphere are eligible for re-treatment with TheraSphere. In these cases, TheraSphere may be administered at the investigator's discretion using lobar infusions on separate treatment days. If such a patient is being treated with sorafenib, sorafenib therapy should be discontinued at least seven (7) days prior through 2 weeks after hours after TheraSphere administration.

TheraSphere should be administered by appropriately trained or designated personnel from the departments of Radiology, Nuclear Medicine, and/or Interventional Radiology.

TheraSphere administration is generally considered to be an outpatient procedure in the United States. It is generally considered to be an inpatient procedure in Europe. The physical location for after-care and

recovery will be determined by individual institutional policies and facility configurations. The location and sequencing of treatment procedure may vary depending on the physical location of the angiography and nuclear medicine suites, the availability of portable gamma cameras, and the clinical judgment of the physician responsible for the treatment plan.

On the day of treatment, an arterial catheter will be placed percutaneously via the femoral or brachial artery under image guidance. The interventional radiologist performs this procedure. The patency of the catheter is maintained by an infusion of normal saline and a coagulation inhibitor (per institutional protocols) administered via a continuous infusion pump. Proper catheter positioning in the selected location in the hepatic artery will be verified on angiography before TheraSphere administration.

Standard medication protocol for sedation, pain and infection prophylaxis should be implemented per established institutional protocols. Prophylaxis with a gastric inhibitor (H2 blocker) is recommended to minimize risk of post-treatment gastrointestinal side effects. Although recommended for all patients undergoing treatment, this prophylaxis is especially important for patients undergoing TheraSphere treatment to the left lobe of the liver, due to the proximity of the gastrointestinal organs, and for patients with a prior history of peptic ulcer disease. Therapy should begin on the day of TheraSphere treatment and continue for 14-21 days following each TheraSphere treatment.

The TheraSphere labeling documents (Appendix 1) describes the specific procedure used to administer TheraSphere.

9.2.15.1.7 THERASPHERE ADMINISTRATION DOCUMENTATION

Any technical problems or complications related to the delivery of TheraSphere treatment to the patient must be documented in the medical record. The details of any event and its impact on the patient should be documented on an Adverse Event eCRF. Patients in the Treatment group must certify continued eligibility prior to administration of TheraSphere. A new blood draw for labs and pregnancy and an ECOG Performance Status test should be performed within 48 hours of administration.

Using institutional practices, the activity of each vial of TheraSphere will be determined prior to administration. This activity will be used to calculate the actual dose delivered to the liver and lung which will be recorded on the appropriate eCRF.

Calculation of the liver dose (Gy) delivered:
Calculation of the delivered dose per infusion takes into account the activity lost to lung shunting plus activity associated with residual microspheres in the administration system and is provided by the following formula:

$$\text{Dose (Gy)} = \frac{50[\text{Injected Activity (GBq)}][1-F][1-R]}{\text{Mass of Selected Liver Target (kg)}}$$

where F = lung shunt fraction (determined in Section 9.2.14.1.3)
R = residual fraction (1-fraction of microspheres delivered)

Calculation of residual activity fraction for microspheres:
The fraction of microspheres remaining in the device is calculated using the following formula:

$$R = \frac{(W-b')}{(I-b)}$$

where R = residual activity fraction

b = background dose rate prior to source vial measurement
I = measured dose rate of source vial positioned greater than 30 cm from ionization chamber (or other measuring device)
b' = background dose rate prior to waste measurement and W = average dose rate of shielded waste container (containing discarded vial, microcatheter, tubing) positioned with center in same location as I

Calculation of Actual Lung Radiation Exposure:
Calculation of the lung dose (Gy) delivered in each infusion is provided by the following formula:

Lung dose (Gy) = 50* activity delivered (GBq)*F

9.2.15.1.8 THERASPHERE POST-TREATMENT PATIENT MANAGEMENT

Immediately following treatment, the patient should remain under observation consistent with institutional SOC guidelines for aftercare in procedures involving femoral or brachial artery catheterization. These aftercare guidelines are unique and subject to the policies and procedures dictated by the respective radiology and radiation safety departments at each institution. Prophylactic treatment using gastric inhibitor (H2 blocker) should continue for 14 – 21 days post treatment. In addition, steroids (e.g., Medrol Dose Pack) may be taken (with food) over the first six days post-treatment.

Prior to discharge, patients should be instructed regarding after-care and provided with a 24-hour telephone number that they may use to contact the Site Investigator if they develop a problem or have questions about their treatment.

Any concurrent medication or therapy deemed necessary, including gastric prophylaxis, to provide adequate supportive care to the patient in the post-treatment period may be administered according to institutional standard of clinical care and should be documented on the Concurrent Medications eCRF.

9.2.15.1.9 RADIATION SAFETY IN THE IMMEDIATE POST-TREATMENT PERIOD

Special radiation isolation procedures for Treatment group patients are not necessary following TheraSphere Treatment. The existence of a small amount of long-lived radioactive byproducts in TheraSphere is a function of the production method[13]: The predominant by-products are Y-91, Y-88 and Cr-51 with respective half-lives of 59, 107 and 28 days. The 3 year accumulated dose to the patient's liver is estimated to be 1/1000 of the planned treatment dose.

Should a patient die or require surgery in the period immediately following-TheraSphere treatment the hospital radiation safety officer should be consulted. At 60 days after the TheraSphere calibration date, a surgeon explanting a treated liver in a procedure lasting one hour would be exposed to an estimated dose to the hands of <0.6 mrem. This is similar to estimated background doses from natural radiation sources which range from 0.5 to 0.8 mrem/day. Institutional radiation safety guidelines for handling of the body and/or body tissues should be followed.

9.2.15.2 SOC SORAFENIB TREATMENT

All patients will receive SOC treatment with sorafenib in accordance with the package insert. Special attention should be paid to patients with hypertension or prolonged QT or at risk of developing QT prolongation (patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking certain anti-arrhythmic medicines or other medicinal products

that lead to QT prolongation, and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia). Blood pressure monitoring plus electrocardiogram with magnesium and calcium laboratory tests done at screening and first post-therapy visit then every 6-8 weeks are recommended. Abnormal results or adverse events related to these conditions observed in study subjects should be recorded as adverse events. Therapies used to manage such adverse events should be recorded in the Concomitant Medication eCRF

Dosage adjustments and drug holidays will be determined to be in the patient's best interest at the discretion of the physician. Consider discontinuing sorafenib if QT/QTc increases over 500ms or increases to 60ms above the baseline reading. All dosage adjustments must be logged on the Treatment Medication eCRF.

Caution is recommended when considering concomitant administration of the following medications; please consult the sorafenib summary of product characteristics/prescribing information for details:

- Warfarin, phemprocoumon or CYP2B6, CYP2C8 and CYP2C9 substrates (monitor regularly for changes in prothrombin time, INR or episodes of clinical bleeding)
- Inducers of metabolic enzymes such as rifampicin, St. John's wort, phenytoin, carbamezepione, phenobarbital, dexamethasone may increase sorafenib metabolism and decrease sorafenib concentrations
- UGT1A1 or UGT1A9 pathways metabolized compounds due to glucuronidation inhibition

Control group patients will start SOC sorafenib therapy as soon as possible after randomization.

Treatment group patients should initiate the SOC sorafenib regimen at least 2 weeks after the completion of TheraSphere administration, and generally from 2 to 6 weeks following completion of TheraSphere administration.

For Patients in the Treatment group who have initiated SOC sorafenib treatment and have progression with hepatic lesions amenable to further TheraSphere treatment, sorafenib should be discontinued seven (7) days prior to the administration of each subsequent TheraSphere treatment. If considered medically appropriate, SOC sorafenib therapy may be resumed after TheraSphere administration, but should only be resumed at least 2 weeks after TheraSphere has been administered.

Sorafenib should be discontinued from seven (7) days prior through 48 hours after each angiographic procedure to reduce the risks of bleeding.

9.2.16 EFFICACY IMAGING – CT/MRI

Baseline efficacy imaging scans will be obtained during screening. Efficacy assessment scans will be taken in accordance with SOC clinical management guidelines every 8 weeks post randomization until death. Most patients will be evaluated by CT images. MRI images are also permitted. The imaging modality used at baseline must continue to be used for all efficacy images throughout the study. Duplicate DICOM images will be submitted to the sponsor or designee to permit future Central Imaging Review in accordance with image submission instructions.

Triple Phase Spiral CT abdomen – must be performed with cuts of 10 mm or less in slice thickness contiguously in the axial plane. From these images, hepatic and extra-hepatic lesions will be read according to the RECIST criteria v1.1 (Appendix 3).

Spiral CT chest and pelvis – must be performed with cuts of 10 mm or less in slice thickness contiguously in the axial plane. From these images, extra-hepatic lesions will be read according to the RECIST criteria v 1.1 (Appendix 3).

For Secondary Study Endpoints based on radiographic assessment, the investigator will identify, read and measure hepatic lesions for size at Baseline using RECIST v 1.1 criteria. At all subsequent follow-up visits, the images (using the same modality) will be read and measured and compared back to the Baseline images and then categorized as Complete Response, Partial Response, Stable, or Progressing at each time point using RECIST v 1.1 (Appendix 3). These data will be captured on the eCRF and may be summarized showing tumor response over time.

The tumor response, according to the mRECIST criteria and based on a blinded centralized independent imaging assessment, will be recorded as an exploratory endpoint. Investigators will not be required to perform mRECIST assessments.

[redacted]

9.2.18 STUDY TREATMENT MEDICATION RECORD

The administration of treatment during the trial will be recorded throughout the trial on the appropriate eCRF. Start/stop dates, dates of change of dosage, and any drug holidays will be recorded.

9.2.19 CONCURRENT MEDICATION RECORD

At every study visit new medications or changes in concurrent medications will be documented on the appropriate concurrent medication eCRF. Documentation will include dosage, start/stop dates, date of change of dosage and any drug holidays.

9.2.20 STUDY COMPLETION

Patients complete the trial upon reaching the primary efficacy endpoint of death. A patient may also decide he/she no longer wishes to participate in the trial. In accordance with the Declaration of Helsinki, and applicable state and federal regulations, a trial subject has the right to withdraw from the study at any time and for any reason. Every effort should be made to have patients complete the study within the provisions of informed consent. However, the participation of the patient may be discontinued at any time during the study when, in the judgment of the investigator, sponsor or subject, it is appropriate.

The reasons for study completion include:

- Death of the patient
- Patient's desire for any reason to withdraw consent
- Administrative reasons
- It is considered necessary by the investigator or sponsor, for any reason

Lost to follow-up is not an adequate reason for withdrawal. Patients should be encouraged to attend study visits until completion of the study or until a decision is taken to withdraw for one of the above-noted reasons.

If intolerance to the study treatment, the patient should be under medical supervision as long as deemed appropriate by the treating physician. Similarly, if study treatment is discontinued due to an AE, the event will be followed until it resolves to the Investigator's satisfaction or is considered stable. The details and reasons for discontinuation must be carefully and completely documented. In either situation, the patient must be followed-up for survival until one of the reasons for study completion is met.

10.0 STATISTICS

10.1 SAMPLE SIZE ESTIMATE

This study is a randomized open label multi-center Phase III adaptive trial using a group sequential design with a primary endpoint of overall survival (OS).

The study is designed to detect a 3.5 month increase in median OS from 10.7 months in the control arm to 14.2 months in the TheraSphere arm (i.e., hazard ratio = 0.754), using a log rank test.

A maximum of 417 deaths will yield 80% power to detect the target difference in median OS (ie, HR=0.754) with a two-sided alpha of 0.05 using a group sequential design with 2 interim analyses and stopping boundary defined by the rho family error spending function with rho=1.5 (Jennison and Turnbull, 2000)[18]. It is estimated that a maximum of 520 patients will need to be recruited over 60 months, with an 18 month additional follow-up period. This includes an adjustment to take account of an assumed 5% of patients who will be lost to follow-up and for whom a date of death is not recorded, and an assumed additional 5% of patients who will be erroneously randomized because they did not meet the eligibility criteria at randomization.

Sample size modification will be considered at the second interim analysis using the approach described in Mehta and Pocock (2011)[16] which employs an un-weighted test statistic at the final analysis as recommended by Burman and Sonneson (2006)[17]. If the sample size is increased after the second interim analysis, the final analysis is planned when approximately, but no less than, 564 deaths have occurred, which will result in 80% power to detect an improvement in median OS from 10.7 to 13.7 months (ie, hazard ratio=0.781) using a log rank test with a final two-sided alpha of 0.0363. It is estimated that approximately 700 patients will need to be recruited over 66 months, with an 18 month additional follow-up period, in order to observe 564 deaths. This includes an adjustment to take account of an assumed 5% of patients who will be lost to follow-up and for whom a date of death is not recorded, and an assumed additional 5% of patients who will be erroneously randomized because they did not meet the eligibility criteria at randomization.

Sample size calculations were performed and verified with PROC SEQDESIGN, SAS 9.3.

[redacted]

10.2 STATISTICAL ANALYSIS PLAN

The statistical analysis plan will be written based on the final protocol and will be updated, as required, in association with any protocol amendments. The plan will include tables, listings and graphs and describe statistical programming considerations.

10.2.1 POPULATIONS AND SUB-GROUPS

- **Modified Intent To Treat population (mITT)**

A modified Intention To Treat (mITT) Population will be used to analyze all efficacy endpoints. This population is defined as randomized patients who met the study eligibility criteria at randomization. The analyses using this population will be performed according to the treatment group to which patients were randomized.

- **Per Protocol Population (PP)**

The PP population comprises patients in the mITT Population without major protocol deviations which may affect the efficacy evaluation. The analyses using this population will be performed according to the treatment actually received.

- **Safety Analysis Population (SA)**

All randomized patients who received study treatments at least once will be included in the safety analysis, and will be analyzed according to the treatment actually received.

- [redacted]

[redacted]

10.2.2 TRIAL ENDPOINTS

10.2.2.1 PRIMARY EFFICACY ENDPOINT

The primary study endpoint is OS which will be calculated as the interval between the randomization date and the date of death for any cause, with censoring at the date of last contact for patients alive at last contact.

10.2.2.2 SECONDARY STUDY ENDPOINTS

Time-to-progression will be compared between the Treatment and Control groups from time of randomization to radiological progression (including new liver lesions and extra-hepatic lesions) according to RECIST v 1.1 criteria by investigator determination.

Time-to-untreatable-progression will be compared between the Treatment and Control groups from randomization to radiological progression (including new liver lesions and extra-hepatic lesions) according to RECIST v 1.1 criteria by investigator determination. For patients randomized to the Treatment group, any liver lesion still amenable to TheraSphere treatment is not considered to be an untreatable progression. Untreatable progression will be defined as one of the following:

- Intolerance to sorafenib

- Occurrence of specific contraindications to sorafenib
- Assessment of progression in the target lesions or occurrence of new lesions after treatment and, for patients randomized to the treatment group, a maximum of 2 re-treatments with TheraSphere
- Occurrence of specific contraindications to TheraSphere and or appearance of lung/intestinal shunts or anatomical constraints not correctable by radiological procedures for the Treatment group.
- Confirmed extra-hepatic metastases
- Deterioration of liver function (Child Pugh score >B7)
- Clinical progression to ECOG performance status >1. Such deterioration in PS should be observed at two subsequent evaluations at 8 week intervals.

Time to symptomatic progression (TTSP): from the time of randomization to ECOG performance status >1 with or without tumor progression based on RECIST v1.1. Deterioration in performance status is to be confirmed at two subsequent evaluations at 8 week intervals.

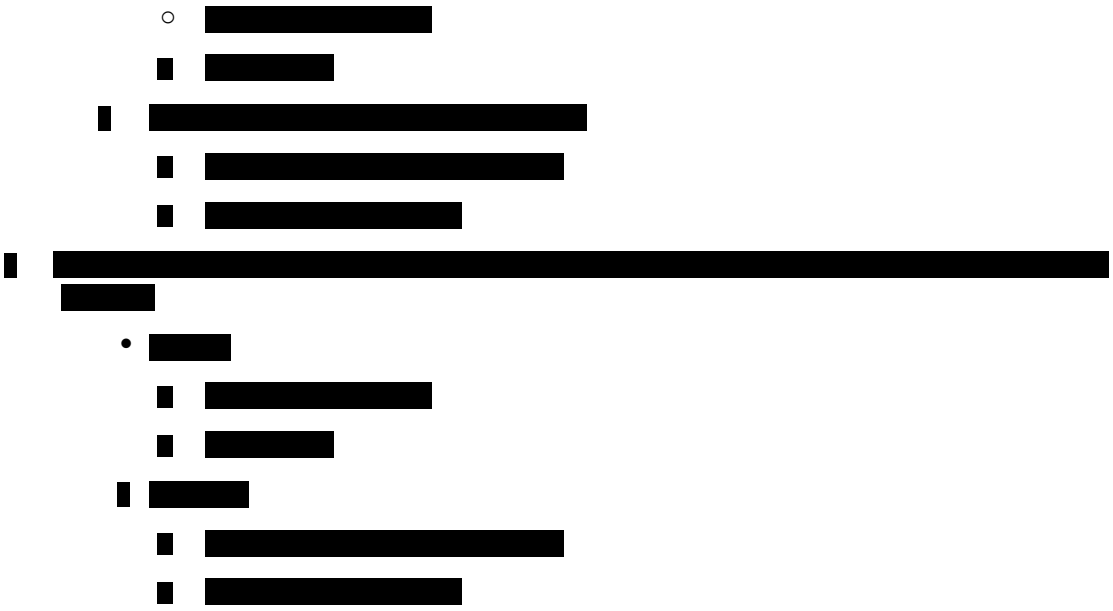
Tumor Response according to RECIST v 1.1 criteria based on investigator assessment. At Baseline, target tumors are identified, read and measured for size. At all subsequent follow-up visits, the images (using the same modality) for the same target lesions will be read and measured and compared back to the Baseline images and then categorized according to the following table:

	RECIST v 1.1
BEST RESPONSE	***Change in the sum of diameter of target lesions***
CR	Disappearance of all target lesions
PR	≥30% decrease in the sum of diameters of target lesions
SD	Neither CR nor PR nor PD
PD	≥20% increase in the sum of the longest diameter of target lesions from the smallest value on study. The sum of diameters must also demonstrate an absolute increase of at least 5mm e.g. Two lesions increasing from 2mm to 3mm does not qualify.

Quality of Life Assessments: Functional Assessment of Cancer Therapy – Hepatobiliary Questionnaire – FACT-Hep. Patients will be asked to complete the questionnaire at Baseline and each of the 8 week study visits.

Safety will be assessed at all visits for enrolled patients using v 4.0 of the National Cancer Institute's Common Terminology for Adverse Events (NCI: CTAE). All adverse events, serious adverse events, and unanticipated adverse device effects as defined by the study protocol will be collected throughout the duration of the study. These events will be documented and recorded on the Adverse Event eCRF using the NCI Common Toxicity Criteria for Adverse Events; CTCAE v. 4.0 standards, and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

[redacted]



10.2.3 EFFICACY ANALYSIS

The efficacy analyses will be performed on the mITT and PP populations.

10.2.3.1 PRIMARY ENDPOINT STATISTICAL ANALYSIS PLAN

Overall survival (OS) time will be calculated as the interval between the randomization date and the date of death for any cause, with censoring at the date of last contact for patients alive. The Kaplan-Meier method will be used to estimate the OS curves in the two treatment groups; comparison between the curves will be performed using the log-rank test.

Interim Analyses: Two interim analyses of OS are planned to be performed by the Independent Data Monitoring Committee (IDMC) based on group sequential stopping rules using an alpha boundary defined by the rho family error spending function with rho=1.5. The first interim analysis is planned at approximately, but no less than, 188 deaths, with a two-sided p-value ≤0.0151 allowing the study to be stopped early for efficacy. A second interim analysis is planned at approximately, but no less than, 250 deaths, with a two-sided p-value ≤0.0151 allowing the study to be stopped early for efficacy.

A conditional power of less than or equal to 15% at each of the interim analyses will result in the study stopping early for futility, using the method described in Proschan et al (2006)[19].

Sample size modification will be considered at the second interim analysis using the approach described in Mehta and Pocock (2011)[16].

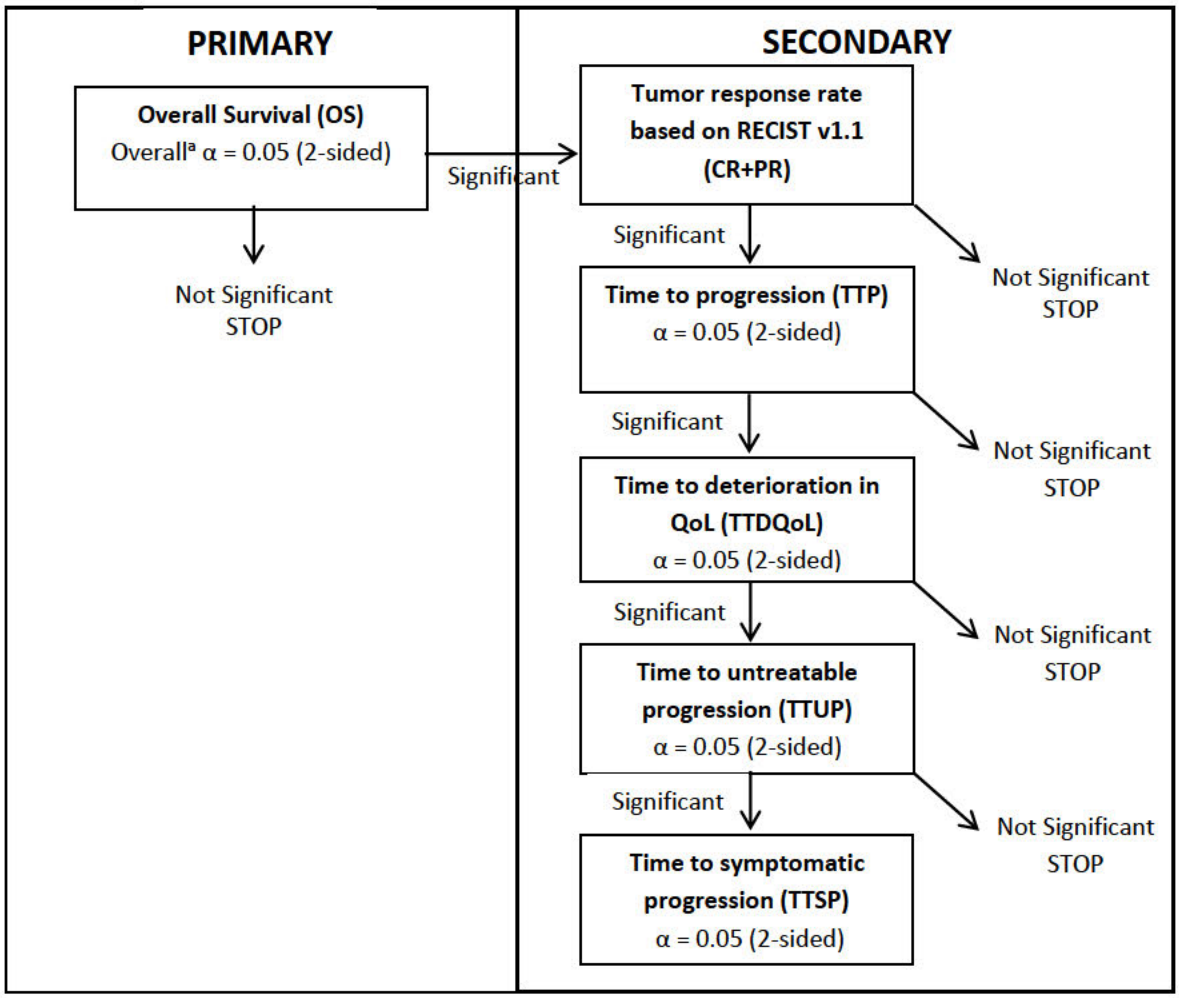
Final Analysis: The final analysis, without a sample size modification, is planned when approximately, but no less than, 417 deaths have occurred. A two-sided p-value ≤0.0363 is required to declare a statistically significant improvement in median OS at the final analysis.

If the sample size is increased after the second interim analysis, the final analysis is planned when approximately, but no less than, 564 deaths have occurred, which will result in 80% power to detect an improvement in median OS from 10.7 to 13.7 months using a log rank test with a final two-sided alpha of 0.0363.

10.2.3.2 SECONDARY ENDPOINT STATISTICAL ANALYSIS PLAN

For secondary efficacy endpoints, each comparison between treatment groups will be conducted at α=0.05 (two-sided). Secondary study endpoints will be analyzed only at the final analysis to determine the statistical significance, if any between, the Treatment and Control groups. Study-wise Type I error will be controlled using a sequential hierarchical approach, as shown in the figure below.

Hierarchical approach to control study-wise Type I error of primary and secondary efficacy endpoints



[a] Type I error is controlled at α = 0.05 (2-sided) over the 2 planned interim analyses and final analysis.

Further supportive analyses of the secondary efficacy time-to-event endpoints using the Cox regression model may be used to evaluate the effect of multiple covariates, including stratification factors.

- Time to progression (TTP) will be calculated as the interval between the randomization date and the date of first disease progression, including the appearance of new lesion(s) and death for any cause or of last contact for patients alive. The Kaplan-Meier method will be used to estimate the TTP curves in the two treatment groups; comparison between the curves will be performed using the log-rank test.

- Time to untreatable progression (TTUP) will be calculated as the interval between the randomization date and the first occurrence of one of the events listed in Section 0. The Kaplan-Meier method will be used to estimate the TTUP curves in the two treatment arms; comparison between the curves will be performed using the log-rank test.
- Time to symptomatic progression (TTSP) will be calculated as the time from randomization to ECOG performance status >1 with or without tumor progression (as defined in Section 0). The Kaplan-Meier method will be used to estimate the TTSP curves in the two treatment arms; comparison between the curves will be performed using the log-rank test.
- Tumor response rate. The response probability will be estimated in each of the two treatment groups as proportion of CR+PR (as defined in Section 0, tumor response according to RECIST v 1.1) over the total number of mITT or PP patients The disease control rate (ie, CR+PR+SD) will also be compared between the treatment arms. Tumor response will be compared using the continuity adjusted Newcombe-Wilson test. The corresponding 95% confidence limits will be calculated.
- Quality of Life. The total score of FACT-Hep will be calculated, the scores of each domain and each question at each time-point and their differences from baseline will be summarized for each treatment group. The two treatment groups will be compared applying a mixed model repeated measures analysis with the treatment, visit and the interaction between treatment as factors, the baseline score as a covariate and further adjusted for the interaction between baseline and visit. A deterioration in QOL is defined as a 7-point decline in the total score or death whichever occurs first. The time to deterioration in QoL (TTDQoL) will be calculated as the interval between the randomization date and deterioration in QoL. The Kaplan-Meier method will be used to estimate the TTDQoL curves in the two treatment arms; comparison between the curves will be performed using the log-rank test

A detailed description of data censoring handling for patients will be defined in the Statistical Analysis Plan.

10.2.4 Safety Analyses

The safety analyses will be performed on the SA population.

All treatment emergent adverse events (TEAEs), defined as events which were not present at baseline or worsened in severity following the start of treatment, will be reported according to NCI Criteria. The incidence of TEAEs will be summarized according to MedDRA coded primary system-organ class (SOC) and preferred term (PT). The summaries will be presented overall (severity grades 1-5) and for grade ≥3 events and by treatment discontinuation. These summaries will present the number and percentage of patients reporting an adverse event for each classification level as well as the number of events reported.

Serious adverse events (SAEs) will be tabulated by treatment group.

Laboratory values will be summarized by treatment group over time and overall.

10.2.4.1 Feasibility Safety Analysis

After the first 20 patients in the Treatment group have received both TheraSphere and sorafenib treatment and completed at least 2 weeks of sorafenib therapy, a feasibility safety assessment will be conducted. The IDMC will review the safety results of both the Control and Treatment groups in an unblinded fashion.

The IDMC will take into consideration the established safety profiles of TheraSphere and sorafenib in this patient population as described in the product labelling, as well as the expected high rates of adverse events and death that are associated with disease progression in patients with intermediate to advanced HCC. The impact of disease progression in these patients may be understood by considering the placebo control data from the SHARP[3] trial, as summarized in the SHARP trial publication and an EMEA[14] overview of sorafenib including a safety review of the SHARP trial data.

A consideration for stopping further enrollment to trial may be made if there is

- An unanticipated patient death definitely or probably related to the sequential administration of TS followed by sorafenib, or
- there is a pattern of serious toxicity clearly related to the sequential administration of TS followed by sorafenib

as assessed by the IDMC experts based on the severity of disease of the enrolled population. Such a toxicity pattern must be clearly different from, or more severe than, what might be expected from independent administration of the products. The potential adverse impact of any such pattern of toxicity on the survival or well being of the patient should be considered in the context of the safety and outcome expectations of patients with advanced HCC.

10.2.5 POOLABILITY AND OTHER ANALYSES

The number of randomized patients, the number of patients treated, the number of patients in each analysis population will be summarized. The number of patients discontinuing from active treatments and reasons for discontinuation will be summarized. In the same manner the number of patients discontinuing follow up and reasons for discontinuations will be reported.

Listings of reasons for discontinuation from active treatments, from follow up, and reasons efficacy data cannot be evaluated in the PP population will be also provided.

Duration of follow up will be described by descriptive statistics such as median and interquartile range.

Demographic, patient and disease characteristics will be listed and summarized using appropriate descriptive statistics.

Multivariate Cox regression analysis of time-to-event efficacy endpoints will be conducted on stratification criteria and other factors such as age, gender, duration of disease prior to randomization to determine the impact of these factors on study endpoints.

As a sensitivity analysis, to address the poolability of data across regions, study sites and gender, a Cox regression analysis of the primary efficacy endpoint, OS, will be conducted with factors of region, study site and gender, and to determine the impact of these factors on OS. Note: region and study site will not be included simultaneously in the model due to collinearity.

Should the impact of region, site or gender on OS be statistically and clinically relevant, the reasons for the observed differential treatment effect, such as patient demographic or clinical characteristics, will be investigated and reported. If the poolability of OS results are in direct question as a result of this sensitivity analysis, the primary endpoint (OS) will also be analyzed separately by region, site or gender. In addition, the primary endpoint (OS) will be analyzed separately by US and non-US region. The specific

mechanism of merging low enrolling study sites into virtual sites for purposes of analysis will be detailed in the Statistical Analysis Plan.

An exploratory analysis will be performed to compare the tumor response rate, based on mRECIST criteria[20] and on a blinded centralized independent imaging assessment, between treatment arms using the continuity adjusted Newcombe-Wilson test.

10.2.6 INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to oversee the conduct of the study, will follow the FDA's Guidance on IDMCs/DSMBs and comply with ISO 14155. The IDMC will meet periodically during the study to review enrollment, protocol deviations, and safety events for the study. In addition, the IDMC will conduct and review the feasibility safety analysis (per Section 10.2.4.1) and will evaluate the data at interim analyses for consideration of stopping the study for overwhelming efficacy or futility and for sample size re-estimation at the second interim analysis. The IDMC will make formal recommendations to the study Sponsor at the time of the feasibility safety analysis, at the time of the interim analyses, and during the conduct of the study based on detailed decision rules specified in the IDMC charter. An IDMC member or designate may act as the study independent medical monitor. The IDMC will evaluate the final study report.

[redacted]

11.0 DATA COLLECTION AND MANAGEMENT

11.1 ELECTRONIC DATA COLLECTION (EDC)

Data from this trial will be captured on electronic case reporting forms (eCRFs), and will be entered into a validated clinical database. An audit trail will be maintained to document all data changes in the database. Procedures will be followed to ensure the validity and accuracy of the clinical database.

The investigator will sign and date all indicated places on the eCRFs. This signature will indicate that thorough inspection of the data has been made and will certify that the Site Investigator has reviewed and approved the data contained on the forms.

11.2 DATA MANAGEMENT

The investigator will ensure that trial data quality is maintained to current standards of Good Clinical Practice and that data are submitted in a timely manner as outlined in the protocol and supporting documentation, including responses to data queries, until the trial is terminated. The investigator must sign an affirmation statement verifying the content of all subjects' eCRFs.

Errors must be corrected in accordance with EDC data entry guidelines.

12.0 ADVERSE EVENTS

Adverse experience will be considered synonymous with the term adverse event and vice versa.

12.1 ADVERSE EVENT DEFINITIONS

Adverse experience will be considered synonymous with the term adverse event and vice versa.

12.1.1 DEFINITIONS OF AE/SAE FOR DRUGS

Adverse Event (AE)

An AE is any untoward medical occurrence or undesirable event(s) experienced in a subject or clinical investigation subject that begins or worsens following administration of the study drug, whether or not considered related to the treatment by the investigator.

An undesirable event(s) can be, but is not limited to, symptoms experienced by a subject or objective findings, such as significant clinical laboratory abnormalities.

Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening ("life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

12.1.2 DEFINITIONS OF ADE/SADE/UADE FOR DEVICES

Adverse Device Effect (ADE)

An adverse device effect is an adverse event (AE – previously defined) related to a medical device and includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment, implantation, installation or malfunction of the device; any event that is the result of user error; or any potential adverse device effect which might have occurred is suitable action had not been taken or intervention had not been made or if circumstances had been less fortunate.

Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (SAE – previously defined) or might have led to any of these consequences if suitable action had not been taken; intervention had not been made or circumstances had been less fortunate.

Unanticipated Adverse Device Event (UADE)

An unanticipated adverse device effect is any serious adverse effect which by its nature, incidence, severity and outcome has not been identified in the risk assessment, the informed consent form as well as the protocol.

12.2 RECORDING ADVERSE EVENTS

All adverse events and adverse device effects will be documented from the date of randomization until study exit. For patients who permanently discontinue sorafenib in either arm of the study, AEs will be documented for 30 days from the date of discontinuation. After this period, only AEs considered to be related to TheraSphere will be collected.

In this study, patients should be encouraged to report adverse events spontaneously or in response to general, non-directed questions. At any time during the study, the patient may volunteer information that resembles an adverse event. Once it is determined that an adverse event has occurred, the Investigator should obtain all the information required to complete the adverse event form. Any medical management of an event and the date of resolution of the event must be recorded in the source document and on the appropriate case reports form(s) using medical terminology according to sponsor instructions.

For each AE, the following information will be recorded:

- Adverse event
- Serious/non-Serious
- Severity (Toxicity Grade)
- Action taken
- Relationship to study treatment
- Expected/Unexpected
- Date and time of onset
- Date and time of resolution

An expected adverse event is any AE, the nature or severity of which is identified in the relevant Package Insert.

Any AE experienced by a subject will be followed until the AE has resolved to the investigator's or physician sub-investigator's satisfaction. If a problem still exists, then the investigator or physician sub-investigator at his/her discretion will ask the subject to come back to the clinic for further evaluation. Any serious adverse events should be managed as discussed in Section 12.3.

Once the subject has been discharged from the study, the investigator has no obligation to seek further follow-up with the subject in order to identify new AEs. However, if the investigator becomes aware of an SAE that has occurred following the subject's discharge from the study and the investigator considers the SAE possibly, probably, or definitely related to a study drug or device, then the investigator should report the SAE as described in the protocol.

12.2.1 CAUSALITY (RELATIONSHIP TO MEDICAL DEVICE) ASSESSMENT

The investigator or physician sub-investigator must indicate whether he/she believes the AE is not related, unlikely related, possibly related (reasonable possibility that the medical device caused the AE), probably related, or definitely related to the medical device.

The Investigator should pay careful attention to the attribution of relation for all adverse events. Because there are many similar events between the TheraSphere and the sorafenib safety profile, judgment of relation by time of administration and patient assignment to treatment or control group should be considered.

An adverse event becomes an adverse device effect when the adverse event is considered associated with the use of the test device if the attribution is Possibly, Probably or Definitely Related. Relation to TheraSphere (screening, procedure, embolization or radiation) is not appropriate for the Control Group. Only those events with a possible, probable or definitely related attribution to TheraSphere will subject to expedited reporting. All other events documented in the trial will be addressed through periodic clinical trial reporting.

12.3 SUBMITTING EXPEDITED SAFETY REPORTS

Any SADE or UADE (defined previously) must be reported by telephone or fax to the sponsoror designate as specified in the study procedures within 24 hours of learning of the event. In the event of an emergency, the Investigator will contact the CRO using the coordinates specified in the study procedures.

The SAE form provided by the sponsor should be completed and signed by the investigator or physician sub-investigator. The entire SAE form needs to be completed, if possible, to keep requests for additional information to a minimum. **Patients experiencing SAE, SADE or UADE should be followed clinically and with laboratory studies, if appropriate, until medical treatment and/or medical monitoring of the event is no longer required because the event resolves or stabilizes, returns to baseline if a baseline value is available, can be attributed to agents other than the study treatments or a referral for appropriate follow-up care has been made.**

The Investigator must promptly inform the IRB of all unexpected SAE or UADE. These events will be reported by the sponsor or it’s designate as appropriate to the regulatory authorities according to relevant jurisdictional medical device regulations. The Investigator will receive notification of these events across all study centers from the sponsor.

Each AE reported on an SAE form must also be reported in the adverse event section of the eCRF.

12.4 PERIODIC SAFETY REPORTING

Adverse events will be recorded on the AE form and coded using NCI CTCAE v 4.0. The investigator or physician sub-investigator will judge the severity of each AE and whether or not it is treatment-related. All AEs that occur after randomization, including events likely to be related to the underlying disease or likely to represent concurrent illness, will be reported, including events present at Baseline which worsened during the trial.

Periodic safety reports prepared by the sponsor will be distributed across all study centers. The Investigator will be responsible for informing the IRB.

12.5 EXPECTED ADVERSE EVENTS

12.5.1 THERASPHERE ADVERSE EVENT PROFILE

TheraSphere has been approved for the treatment of HCC since 1999. Adverse events known to be related to the device or the procedure listed in the current package insert (Appendix 1). Those adverse events identified in clinical trials investigating treatment with TheraSphere of liver lesions metastatic to non-HCC primary cancers are listed below in decreasing order of frequency.

Frequency	Description of Adverse Event (per NCI-CTCAE v 3.0)
Common - >10%	Fatigue, pain, nausea, vomiting, anorexia and laboratory value abnormalities including increased alkaline phosphatase, AST, ALT, bilirubin and decrease albumin
Infrequent - <10%	Lymphopenia with no clinical sequelae; constipation, heartburn, weight loss, fever, ascites, muscle weakness, variations in hemoglobin, neutrophils and leukocytes, GI ulcer, dyspnea, arrhythmia, diarrhea, liver dysfunction, hypotension, insomnia, rigors/chills, sweating, distension, GI obstruction, hematoma, GI hemorrhage, pleural effusion
Rare – < 1%	Alopecia, bruising, pruritis, rash, hot flashes, dehydration, taste alteration, hemorrhage, infection, dizziness, mood alteration, sensory neuropathy, somnolence, cough, urine color change, intraoperative injury, flu-like symptoms, tumor lysis syndrome, thrombosis, metabolic/laboratory abnormalities – creatinine, hypercalcemia, hyperglycemia, hyperkalemia, hypermagnesemia, lipase

In addition, the following events, which may or may not be related to the use of TheraSphere or the administration procedure, have been reported in clinical trials of treatment of primary or secondary liver cancer:

Abdominal pain, dyspnoea, abdominal distention, anxiety, blurred vision, chills, hot flashes, bladder infection, lower extremity edema, gastrointestinal stoma complication including mild pain, hepatic encephalopathy, hepatorenal failure, edema, malaise, hepatic decompensation, hepatitis, duodenal ulcer, hypertension, hypertension, aspiration pneumonia, fall, gastrointestinal bleeding, elevated AFP, elevated LDH, elevated prothrombin time, elevated BUN, bacterial sepsis, hypoglycemia, abnormal platelets and electrolyte disturbances including hypercalcemia, hyperkalemia, hypomagnesemia, hyponatremia, low serum bicarbonate and low serum chloride.

12.5.2 SORAFENIB ADVERSE EVENT PROFILE

Sorafenib has been approved for treatment of HCC since 2007 and adverse events known to be related to this therapy are listed in the current package insert. Safety updates to the commercial package insert by the manufacturer automatically apply to this trial.

13.0 INVESTIGATOR AND SITE QUALIFICATION AND OBLIGATIONS

13.1 STUDY SITE AND INVESTIGATOR QUALIFICATION

This study will be performed by qualified investigators at multiple research centers in the United States, Canada, Europe, and Asia.

All participating study sites will be reviewed by the study Sponsor or designee in order to verify that they are able to conduct the trial. Each participating institution must have an established IRB and clinical protocol review process in compliance with the appropriate regulations (21 CFR 56 or ISO 14155) so the clinical protocol can be adequately evaluated and approved at the institutional level.

The institution must have appropriately qualified investigators, and clinical and administrative support staff in place to adequately conduct the trials according to GCP in general, and must have adequate expertise and staff in the treatment of patients with hepatocellular carcinoma and the ability to adequately conduct clinical research under Good Clinical Practice Standards (GCP) consistent with the regulations of 21 CFR 812, Investigational Device Exemptions, and ISO 14155.

In addition, all participating study sites must be appropriately experienced in the use of Y-90 microspheres for the treatment of liver tumors, and must have completed adequate training in order to use the TheraSphere Y-90 microsphere product. The required training will be specified by the sponsor. Generally, an adequate level of experience consists of a minimum of five (5) TheraSphere administrations for sites without radioembolization experience and at least three (3) administrations of TheraSphere for sites experienced in radioembolization with different radioactive microsphere product.

13.2 INSTITUTIONAL APPROVAL AND DOCUMENTATION OF THE PROTOCOL

Prior to initiating the clinical study, each participating institution must have documentation that the Institution Review Board (IRB) has reviewed and approved the protocol and the Informed Consent Form (ICF).

The final IRB approved protocol, consent form, documentation of IRB approval of the consent and protocol, Study Contract, Statement of Investigator, CVs of all investigators and study coordinators, records of protocol training, and all other study-related required regulatory documentation as described in the Sections below must also be maintained in the clinical study files for this trial.

The Site Principal Investigator is ultimately responsible for ensuring that required study documentation has been obtained, that all study procedures are properly followed, and that all enrolled patients meet the eligibility criteria prior to enrollment under this protocol.

The Investigator is responsible for submission of the protocol, informed consent form, any patient education materials, and any recruitment or advertising materials and the institution's IRB.

- Written approval of the protocol and Informed Consent Form must be obtained prior to recruitment of patients into the trial at each site and prior to administration of protocol treatment to any randomized patient.

- Written approval of the recruitment and advertising materials must have IRB approval before use.

- The Investigator is responsible for obtaining and maintaining IRB approval at his facility and providing copies of all IRB correspondence to the Sponsor or designee.

This protocol is a multi-center protocol and as such must remain consistent with all other sites.

13.3 REGULATORY DOCUMENTS

The following documentation must be obtained before study enrollment can begin (with the exception of Final Report).

- Institutional Review Board Approval

A copy of the protocol and any amendments, the proposed informed consent form (ICF), other written subject information and any proposed advertising material must be submitted by the Investigator to the IRB for written approval. A copy of the written approval of the protocol and ICF must be received by the sponsor or designee before recruitment of subjects into the study and administration of protocol treatment.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The investigator should notify the IRB of deviations from the protocol and SAEs as required by local procedures.

The investigator will be responsible for updating the IRB about the status of the trial at least annually and obtaining any required approvals renewal throughout the duration of the study. Copies of any correspondence and other documentation between the investigator and the IRB must be retained as part of the site documentation of the study. Copies of all such documents must be sent to the sponsor or designee.

- Institutional Review Board Membership Roster

The investigator must submit a complete and current roster of the IRB to the sponsor or designee. Some institutions, on grounds of confidentiality, may not release the IRB roster. In such instances, the institution's General Assurance Number, assigned by the Department of Health and Human Services, is an acceptable substitute.

- Statement of Investigator

The investigator will be required to sign and date a Statement of investigator form provided to them by the sponsor. A copy of this form will be given to the investigator for their files. The original form will be maintained by the sponsor.

- Curriculum Vitae

The investigator will provide the sponsor or designee with his/her up-to-date curriculum vitae (to within two years throughout the duration of the trial) and those of any sub-investigators or staff personnel with significant trial responsibilities.

- Laboratory Certification and Normal Values

The Investigator will provide the sponsor with the name and location of the clinical laboratory to be utilized for determination of laboratory assays, copy of certification and a list of the normal range of values of all laboratory tests. Any changes in laboratory, certification or normal ranges will be communicated promptly to the sponsor or designee.

- Financial Disclosure

Financial disclosure statements will be completed for the investigator and all sub-investigators to disclose potential conflicts of interest (per 21 CFR 54 and ISO 14155). The investigator is responsible for ensuring completed and signed financial disclosure forms, which are provided by the sponsor or designee. A copy of the form(s) will be given to the investigator for their files. The original form(s) will be maintained by the sponsor Financial disclosure information will be collected by the sponsor before the start of the study and maintained for one year after study completion.

- Final Report

Upon completion of the clinical trial, a final study report will be provided by the sponsor; The Investigator will prepare and submit to the IRB a final report, including final study report.

13.4 SOURCE RECORDS AND STUDY DOCUMENTATION

Investigators are required to prepare and maintain adequate source documentation. Source documentation includes:

- documents relative to the patient's medical history that verify the eligibility criteria
- records covering the patient' participation in the study which include but are not limited to basic identification information, results of physical examinations and diagnostic tests, therapy, device administration, concurrent medication information and visit/consult notes.

The Investigator will initial and date all laboratory reports or initial and date statements at each study visit that all clinical laboratory data was reviewed.

Federal regulations concerning the period during which study records must be maintained by the Investigator vary from country to country. Investigators are required to comply with their local regulatory authority for storage of study documentation. For the purpose of this study the minimum retention for Study Documentation is a period of two (2) years after the later of the following: (a) date on which the Study is terminated or completed; or (b) date records are no longer required to support a premarket approval application, notice of completion of a product development protocol, or other application for research or marketing permit.

Completed eCRFs that are dated and signed by the investigator must be made available for review and retrieval by the sponsor or designee at the time the subject completes the study. The sponsor or designee will provide the investigator with a copy of completed eCRFs for their files.

In order to ensure the accuracy of data collected in the eCRFs, it is mandatory that representatives of the sponsor, as well as representatives of a regulatory agency (eg, the Food and Drug Administration) or the institutional review board (IRB), have access to source documents (ie, subject records, subject charts, and laboratory reports). During the review of these documents, the anonymity of the subject will be maintained with strict adherence to professional standards of confidentiality. The sponsor reserves the right to terminate the study for refusal of the investigator to supply source documentation of work performed in this clinical trial.

13.5 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with standard operating procedures of the sponsor or designee, which are designed to ensure adherence to good clinical practice (GCP) guidelines as required by the following:

1. World Medical Association (WMA), Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and as amended at subsequent WMA General Assembly meetings.

2. E6 Good Clinical Practice: Consolidated Guidance (International Conference on Harmonization of Pharmaceuticals for Human Use [ICH], April 1996 governing drugs and ISO 14155 governing devices.

3. Title 21 of the Code of Federal Regulations (21 CFR) Parts 50, 54, and 56.

13.6 RESPONSIBLE CONDUCT OF RESEARCH

The Sponsor will ensure that this trial is conducted in full conformity with the current revision of the 'Declaration of Helsinki', ISO 14155, the U.S. Code of Federal Regulations 21 CFR 812, and applicable state and federal regulations, whichever affords the greatest protection to the patient. The Sponsor is responsible for providing monitoring oversight for the study to ensure the involvement of the Investigator in the trial, to ensure the rights, safety and well-being of the patients, compliance to the protocol and to all applicable laws, and to oversee the completeness, accuracy and consistency of the data collected in support of a premarket approval application.

The procedures defined in the protocol and the eCRFs will be carefully reviewed by the Sponsor with the Investigator and staff prior to time of trial initiation to ensure appropriate interpretation and implementation. No deviations from the protocol may be made without advance approval from the sponsor and the IRB as required by the policies of the IRB.

Monitors from the Sponsor, or their designees, will periodically visit the site to review case report forms, the Regulatory Binder, patient medical records including electronic records, imaging files, laboratory reports, device accountability, site training and authorization of delegation and any other records related to the study conduct. Investigator will maintain and release the records for review, provide access to the records and copies as needed, and will meet with the monitor as needed to discuss study progress and

needs. The Investigator should maintain the files suitable for inspection at any time by a trial monitor from the sponsor, or the appropriate regulatory authority, or designate representing these organizations.

13.7 INFORMED CONSENT

An IRB approved signed informed consent form (ICF) must be obtained from a patient before that patient can enter the trial, and before any study related evaluations can be performed on that patient.

The investigator is responsible for the creation of the ICF and must ensure that the informed consent adheres to the U.S Code of Federal Regulations, 21 CFR 50, ISO 14155or equivalent, as appropriate to his/her country. The Investigator will ensure that the local IRB has approved the protocol and the informed consent prior to the initiation of the trial. The signed informed consent from each patient must be kept in the patient's study file.

The investigator or designee will review the treatment plan with the patient and the patient will have an opportunity to ask questions regarding study procedures, the required visit schedule, risks/benefits of the use of the approved device (TheraSphere), and alternative treatment options prior to signing the ICF. The patient will receive a copy of the signed informed consent to keep for their records. Periodically during the study, revisions to the informed consent form may be needed. Patients will be informed of such revisions and any revisions must be signed and kept in the patient's study file.

The acquisition of informed consent should be documented in the subject's medical record and the ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily by the investigator).

Patients for whom English is not their first language may need a written translation of the document and/or a patient advocate, according to the policies of the IRB. The Investigator will provide the sponsor a copy of the IRB approved translation, if any.

13.8 PATIENT MEDICAL RECORDS

The Investigator must maintain adequate medical records regarding their care of the patient, including case histories, to support the clinical data in the case report forms. These records must be maintained and made available for monitoring and auditing by the Sponsor, or their designee, and the appropriate regulatory agency. All CT/MRIs will be maintained or archived along with the medical chart for review for at least 2 years after premarket approval of the device.

13.9 PATIENT PRIVACY AND CONFIDENTIALITY

All collected patient data will be treated confidentially. Patients will be identified anonymously and in accordance with national laws and regulations. Medical records relating to this trial, including those that are electronically maintained and those that may contain information that would identify an individual patient will remain confidential, but may be reviewed by, released, and/or transmitted to representatives of the hospital, the appropriate regulatory agency, the Sponsor or its agents, and the Independent Data Monitoring Committee when reasonable and appropriate for the conduct of the trial.

As part of the required content of the informed consent, the patient must be informed that his/her records will be reviewed by the sponsor and/or a representative of the appropriate regulatory agency and the Independent Data Monitoring Committee. The informed consent or related document will also state

that patient privacy will be maintained pursuant to the Health Insurance Portability and Accountability Act (HIPAA), 21 CFR 21 or equivalent for countries other than the United States. Should access to the medical record require a separate HIPAA waiver or authorization per institutional confidentially policies, it is the Investigator's responsibility to obtain such permission from the patient in writing before the patient is entered into the trial.

13.10 Additional Investigator Responsibilities

Additional Investigator responsibilities are noted in ISO 14155and in Section 11 of the US 21 CFR 812.100, 812.110 and in country-specific guidelines and laws and responsibilities for reporting of unanticipated adverse device events and deviations from the investigational plan per 812.150 as well as the following:

- Ensure compliance with institutional and appropriate relevant jurisdictional Radiation Safety policies and procedures
- Assemble and coordinate a team that includes a designated co-investigator in all of the medical disciplines necessary for the efficient conduct of the protocol (oncology, interventional radiology, nuclear medicine, diagnostic radiology, etc).
- Provide a trial coordinator who will be responsible for assisting the Investigator in meeting data collection and reporting requirement and for scheduling, management and follow-up of trial patients.
- Provide adequate access to study materials for the sponsor to monitor the trial at appropriate and convenient intervals and provide an adequate, secure area, within the study site facility for the sponsor representative to conduct these monitoring activities.

14.0 Protocol Deviations

It is vital to the success of the study that the investigator adheres to the details of the protocol. A protocol deviation is any change, divergence or departure from the study protocol regardless of the consequences to the patient or study outcomes.

15.0 Major and Minor Protocol Deviations

A major protocol deviation is defined as a divergence from the protocol that materially (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare, example:

- Enrollment Violations
- Eligibility criteria deviations
- Inadequate informed consent Intentional repeated deviations from the protocol
- TheraSphere Administration Violations: TheraSphere treatment dose outside the range of 90-120 Gy ± 10%
- Post-Treatment Violations: Administration of any liver-directed local regional therapy, except as specified by the protocol, following intra-hepatic progression.

A minor protocol deviation is defined as a divergence from the protocol that is without significant consequences to the patient and the study data. An example is missing a visit window because a patient is traveling.

16.0 STUDY MONITORING

The study will be monitored by qualified personnel from the sponsor or a contract research organization (CRO) contracted to provide such monitoring by the sponsor. Data management and statistical analyses will be the responsibility of the sponsor who will contract with one or more organizations to manage these functions.

Before initiation of the trial, representatives from the sponsor will, together with the investigator, review the protocol and the facilities. At trial initiation, the sponsor's representative will thoroughly review the protocol and go over the eCRFs and electronic data entry procedures with the investigator(s) and other authorized staff.

During the course of the trial, a study monitor or other authorized representatives of the sponsor will visit the investigator at suitable intervals. The purpose of these visits will be to verify compliance with applicable government regulations and adherence to the protocol, ensure correct completion of the eCRFs.

In order to perform his/her role effectively, the study monitor(s) must be given access to source documentation (eg, clinic charts, original laboratory records), which support data on the eCRF, and informed consent forms. The monitor must be able to verify data appearing in the eCRFs against data in the subject's clinic chart (eg, chart notes) or in printout forms (eg, laboratory results).

17.0 STUDY TERMINATION

The sponsor reserves the right to discontinue this study for administrative reasons at any time. The end of the study is defined as the reaching of the required number of deaths and all TheraSphere treated patients have been followed-up for a minimum of 30 days from the last TheraSphere treatment, and all sorafenib treated patients in the control arm have been followed-up for a minimum of 30 days after the last dose of sorafenib.

APPENDICES

1. TheraSphere Product Labeling
    a. US Package Insert
    b. CA Package Insert
    c. EU Instructions for Use

2. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol. 2006 Aug; 17(8):1251-78. Review. Erratum in: J Vasc Interv Radiol. 2006 Oct; 17(10):1594.

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4. Child Pugh Classification

   Assess severity of liver disease by assigning points for each of the five parameters in the table below and adding the points to obtain a total score. Record the resulting Child Pugh Grade: A (well compensated disease) 5-6 points; B (functional compromise, worsening disease) 7-9 points and C (decompensated disease) 10-15 points.

Parameter	**1 point**	**2 points**	**3 points**
Bilirubin	<34 µmol/L	34–50 µmol/L	>50 µmol/L
Albumin	>35 g/L	28-35 g/L	<28 g/L
Prothrombin Time	<1.8 (INR) or <4 secs (Seconds over control)	1.8-2.2 (INR) or 4-6 secs	>2.2 (INR) or >6 secs
Ascites	absent	Slight (medically controlled)	Moderate (poorly controlled)
Encephalopathy*	None	Grade 1-2	Grade 3-4

*Grades of Encephalopathy

Grade 1 – Inverted sleep pattern; forgetfulness, agitation, irritability, apraxia

Grade 2 – Lethargy; Disorientation for time or place, Subtle personality change; Asterixis, ataxia

Grade 3 – Somnolence but rousability; Disorientation as regards place; Asterixis, hyperactive reflexes, Babinski signs, muscle rigidity

Grade 4 – Coma (unresponsive to verbal or noxious stimuli)

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