Protocol Number:	TS-104
Protocol Short Title:	YES-P
Protocol Name:	A prospective randomized clinical trial on ^{90}Yttrium trans-arterial radio-Embolization (TheraSphere®) vs. Standard of care (sorafenib) for the treatment of advanced Hepatocellular Carcinoma (HCC) with Portal Vein Thrombosis (PVT)
Global Sponsor:	Biocompatibles UK Ltd Chapman House Farnham Business Park Weydon Lane, Farnham Surrey GU9 8QL, UK (Biocompatibles)
Global Principal Investigators	[redacted] Italy [redacted] USA [redacted]
Medical Monitor:	[redacted] Theorem Clinical Research, Inc. 35 Nieklanska St. 03-954 Warszawa, Poland [redacted]
Device:	TheraSphere®, Yttrium-90 Glass Microspheres
CE Mark for EU sites only	CE 0086
HDE # for US sites only:	HDE H980006
Protocol Date Activated:	2012/06/22 (YYYY/MM/DD)
Amendments:	Version 1.1 Dated 2012/09/28 Version 2.0 Dated 2013/09/13 Version 3.0 Dated 2014/08/08

PROTOCOL APPROVAL AND RELEASE SIGNATURE PAGE

Protocol Title: A prospective randomized clinical trial on ^{90}**Y**ttrium trans-arterial radio-**E**mbolization (TheraSphere®) vs. **S**tandard of care (sorafenib) for the treatment of advanced Hepatocellular Carcinoma (HCC) with **P**ortal Vein Thrombosis (PVT)

Protocol #: TS-104

Protocol Approval Date: Version 1.0 2012-06-07 (YYYY/MM/DD)

Version 1.1 2012-09-23
Version 2.0 2013-09-13
Version 3.0 2014-08-08

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

Principal Investigators

[redacted]

Signature **Date (YYYY/MM/DD)**

[redacted]

Signature **Date (YYYY/MM/DD)**

Biocompatibles UK Ltd.

[redacted]

Signature **Date (YYYY/MM/DD)**

[redacted]

Signature **Date (YYYY/MM/DD)**

INVESTIGATOR'S PROTOCOL REVIEW STATEMENT

By my signature, I confirm that my staff and I have carefully read and understand the protocol, A prospective randomized clinical trial on ^{90}**Y**ttrium trans-arterial radio-**E**mbolization (TheraSphere®) vs. **S**tandard of care (sorafenib) for the treatment of advanced Hepatocellular Carcinoma (HCC) with **P**ortal Vein Thrombosis (PVT), 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 (YYYY/MM/DD)

_____

Investigator Printed Name

TABLE OF CONTENTS

1 PROTOCOL SYNOPSIS

Protocol Title	A prospective randomized clinical trial on ^{90}Yttrium trans-arterial radio-Embolization (TheraSphere®) vs. Standard of care (sorafenib) for the treatment of advanced Hepatocellular Carcinoma (HCC) with Portal Vein Thrombosis (PVT)
Type of Protocol	Phase III protocol to collect efficacy and safety data
Protocol Design	This is a two-arm, open-label, prospective, multi-center, randomized, active-controlled clinical trial.
Study Objective	To assess efficacy and safety of TheraSphere in comparison to standard of care therapy (sorafenib) in the treatment of patients with portal vein thrombosis associated with unresectable hepatocellular carcinoma.
Primary Endpoint	Overall Survival (OS) from time of randomization
Secondary Endpoints	• Time to progression (TTP) from time of randomization based on investigator assessment according to RECIST v 1.1 • Time to progression (TTP) from time of randomization based on investigator assessment according to modified RECIST • Time to progression (TTP) from time of randomization based on investigator assessment according to EASL response criteria • Time to worsening of PVT from time of randomization to the time of any change in the classification of PVT type by at least one sub-type (see Section 9.2.5) based on investigator assessment • Time to symptomatic progression (TTSP) from the time of randomization to assessment of ECOG performance status ≥2 with or without tumor progression based on imaging. Deterioration in performance status is to be confirmed at one subsequent evaluation 8 weeks later. • Tumor response according to RECIST v 1.1 criteria based on investigator evaluations • Tumor response according to modified RECIST criteria based on investigator evaluations • Tumor response according to EASL response criteria based on investigator evaluations • Patient reported outcome (PRO) as assessed by the Functional Assessment of Cancer Therapy – Hepatobiliary Questionnaire (FACT-Hep) questionnaire • Adverse events (NCI-CTAE v 4.0)
Trial Population	Patients diagnosed with portal vein thrombosis associated with unresectable advanced HCC, who are not eligible for any curative procedure.
Number of patients	Approximately 320 patients randomized planned, with up to a maximum of 500 patients randomized based on sample size re-estimation
Number of sites	Up to 25 sites in Europe, Asia and North America
Protocol Treatments	• The Control arm will receive standard-of-care (SOC) therapy sorafenib in accordance with the approved product labeling.

	• The Treatment arm will receive TheraSphere in accordance with the approved product labeling.
Study Duration	Approximately 42 months of accrual and 1 year additional follow-up are planned (with up to a maximum of 72 months of accrual based on sample size re-estimation).
Eligibility Criteria	1. Patients over 18 years of age, regardless of race or gender 2. Advanced stage HCC confirmed by histology (mandatory in non cirrhotic patients) or non-invasive criteria (EASL/AASLD) with branch PVT. o Either naïve or recurrent HCC after curative treatment (minimum 3 months from curative treatment - minor resection or local ablation) is acceptable. o Branch PVT classified as Type I, Type II or Type IIIa (see Section 9.2.5). 3. Unilobar disease as defined in Section 8.1. 4. Tumor volume ≤ 70% of liver volume (determined by visual estimation) 5. Child-Pugh A 6. At least one uni-dimensional HCC target lesion assessable according to the RECIST v1.1 criteria by CT-scan or MRI 7. No confirmed extrahepatic metastases. Patients with indeterminate hepatic hilar lymph nodes up to 2.5 cm in greatest dimension, or with indeterminate lung nodules (single lesion between 1-1.5cm, or multiple smaller lesions with a total diameter ≤ 2 cm) may be included if metastatic disease is deemed unlikely 8. No known contraindications to standard-of-care sorafenib including allergic reaction, pill swallowing difficulty, uncontrolled hypertension or history of cardiac disease (according to sorafenib package insert and country-specific policies, may include evidence of severe or uncontrolled systemic diseases, cardiac arrhythmias (requiring anti-arrhythmic therapy or pace maker), congestive cardiac failure >New York Heart Association class 2, myocardial infarct within 6 months, prolonged QT/QTc >450ms), 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, renal failure requiring dialysis 9. No evidence of hepatic vein invasion or caval thrombosis 10. Cancer-related symptoms within the ECOG 0-1 category 11. PLT ≥ 50 x10^3/µL 12. WBC ≥ 1.5 x10^3/µL 13. AST/ALT ≤ 5 times the upper limit of normal (U/L) 14. Creatinine ≤ 2.0 mg /dL 15. No evidence of pulmonary insufficiency or clinically evident chronic obstructive pulmonary disease. 16. No indication for any possible curative treatment after multidisciplinary assessment (surgery, ablation, transplantation) 17. No previous treatment with Sorafenib for more than 4 weeks during the 2 previous months; no prior sorafenib-related toxicity at any dose and/or duration defined as documented sorafenib-related grade 3 or 4 adverse events that led to sorafenib discontinuation

	18. No initiation of any other anti-tumor therapy including chemotherapy, radioembolization (maximum lung shunt of 20% for prior radioembolization) or investigational drug treatment within 30 days before the beginning of the study 19. In case of patients progressing from an intermediate to an advance stage because of occurrence of PVT, enrolment is allowed if previous conventional or drug eluting TACE was performed at least 3 months prior to screening phase 20. Patients cannot be on a liver transplantation list 21. No history of organ allograft 22. No contraindication to angiography or selective visceral catheterization 23. No history of severe allergy or intolerance to contrast agents, narcotics, sedatives or atropine that cannot be managed medically 24. No previous external beam radiation treatment to the liver 25. No evidence of continuing adverse effect of prior therapy 26. No active GI bleeding and any bleeding diathesis or coagulopathy that is not correctable by usual therapy or hemostatic agents (e.g., closure device) 27. No evidence of any disease or condition that would place the patient at undue risk and preclude safe use of microspheres (TheraSphere®) treatment 28. Negative serum pregnancy test in females of child-bearing potential; patients who are breast-feeding cannot participate in this trial 29. Life expectancy of greater than 3 months 30. No participation in concurrent interventional clinical trials 31. Signed informed consent form
Imaging Requirements	• Triple Phase CT abdomen/pelvis – performed with cuts of 10 mm or less in slice thickness contiguously in the axial plane. To assess disease extension and to determine liver volume measurement and identify hepatic vascular anatomy. • Spiral CT Chest –(with contrast media in case of CT abdomen/pelvis and without contrast media in case of MRI abdomen/pelvis) 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 abdomen/pelvis; however, the same imaging modality should be used for all images in an individual patient throughout the study • Hepatic angiography and 99mTC-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 99mTC-MAA may be needed to estimate cumulative lung shunt or re-asses GI flow. • Bone scintigraphy to assess metastatic disease in patients with AFP > 400ng/mL • SPECT imaging may be performed according to standard of care practices for clinical management but is not a study requirement.
Sample Size Calculation and Statistical Plan	This study is an adaptive trial using a group sequential design with overall survival (OS) as the primary efficacy endpoint.

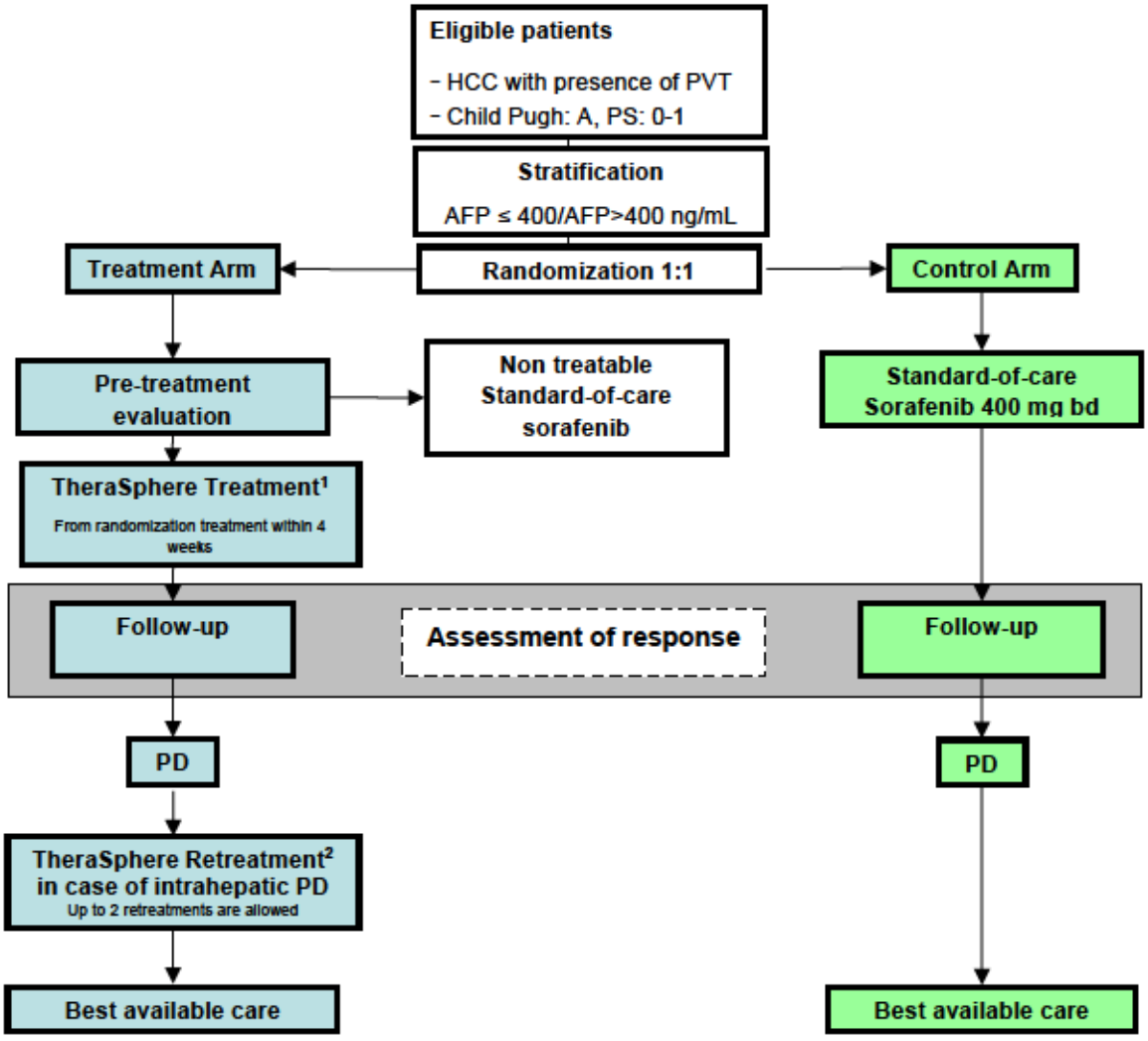
	The study is designed to detect a 4 months increase in median OS time, from an anticipated value of 9.0 months in the sorafenib arm to 13.0 months in the TheraSphere arm (ie, hazard ratio = 0.69), using a log rank test. Due to uncertainty in the expected treatment effect, a sample size re-estimation is planned, which would allow the sample size to increase to detect a 3 month improvement in median OS in the TheraSphere arm as compared to the control arm (ie, HR = 0.75). A maximum of 250 deaths will yield 80% power to detect the target difference in median OS (hazard ratio = 0.69) with a two-sided alpha of 0.05 using a group sequential design with 2 interim analyses. It is estimated that a maximum of 320 patients will need to be recruited over 42 months, with a 1 year 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. 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 will be performed when approximately, but no less than, 125 deaths have occurred, with a two-sided p-value ≤0.0177 allowing the study to be stopped early for efficacy. A second interim analysis will be performed when approximately, but no less than, 188 deaths have occurred, with a two-sided p-value ≤0.0228 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), which employs an un-weighted test statistic at the final analysis as recommended by Burman & Sonneson (2006). Final analysis of primary endpoint: The final analysis, without a sample size modification, will be performed when approximately, but no less than, 250 deaths have occurred. A two-sided p-value ≤0.0322 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, 430 deaths have occurred, which will result in 80% power to detect an improvement in median OS from 9 to 12 months using a log rank test with a final two-sided alpha of 0.0322. 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, TTSP, Time to worsening of PVT) 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 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 . Laboratory values will be summarized by treatment group over time and overall. 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 (ie, Europe, North America, Asia), 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.
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, images and test results obtained for clinical patient management within the number of days before randomization specified in Section 9.1.1 and before signing of informed consent may be used for screening assessment), • Demographics • Physical examination • Medical history • Categorization of PVT based on dynamic imaging studies • Child-Pugh assessment of chronic liver disease • ECOG Performance Status assessment • Abdomen/pelvis spiral CT/MRI to assess liver tumor presentation, calculate liver volume and assess tumor burden in the liver. • Chest CT to rule out extra-hepatic metastases • Bone scintigraphy if AFP > 400ng/mL • Baseline FACT-Hep Patient Reported Outcome questionnaire • Required laboratory blood work plus alfaphetoprotein (AFP) The date of screening is the date all screening procedures are completed.
Randomization	Upon meeting eligibility for study participation in accordance with the Inclusion/Exclusion criteria, patients will be randomized 1:1 to Treatment and Control

	Arms. In order to balance the treatment arms, patients will be stratified at randomization on the basis of • Serum level of alfaphetoprotein (AFP) (≤ 400 ng/ml vs > 400 ng/ml) • Participating trial site
Control Arm Study Treatment(Sorafenib)	All patients randomized to the Control arm should start treatment with standard of care sorafenib within 2 weeks from 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 Arm Study Treatment (TheraSphere)	Within 2 weeks from 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 or to perform tumor redistribution so that the patient can meet eligibility criteria. Patients will not be eligible for TheraSphere infusion 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, dose reduction of TheraSphere is permitted (minimum dose allowed is 80 Gy ± 10%). These patients will be eligible to receive sorafenib SOC therapy and will be included in the Treatment Arm Intent-to-Treat analysis, but not in the Treatment Arm Per-Protocol analysis. TheraSphere Treatment: TheraSphere treatment should occur within 28 days of randomization. The number of infusions required to achieve lobar treatment will be determined by the Investigator, based on the hepatic vascular anatomy. Patients will receive TheraSphere, at a dose consistent with the approved product label, to the treated lobe of the liver. A target dose of 120 Gy ± 10% is advised.TheraSphere Re-treatment: Re-treatment of the same patient/lobe with further cycles of TheraSphere is permitted if a treatable progression is detected during follow-up evaluations. Any re-treatment should take place at least 28 days from the last TheraSphere treatment administered to that lobe. Patients can receive a subsequent TheraSphere administration in the absence of radiological progression criteria at investigator discretion. Patients must meet initial eligibility criteria to receive subsequent treatments. A maximum of three (3) TheraSphere administrations are permitted in total.
Study Visits and Follow-up	Study visits that take place after the screening/randomization period should occur within +/- 7 days of the designated time interval for that study visit. Screening evaluations will be completed within 14 days prior to randomization. Images and test results obtained for clinical patient management and before signing of informed consent do not need to be repeated and may be used for screening assessment provided images were taken within 28 days and tests conducted within 14 days of randomization. These evaluations will be the baseline values for patients randomized to the trial. For patients randomized to Standard of care Sorafenib, study visits will take place at least once every 4 weeks until progression then every 8 weeks for as long as the patient remains on the trial. Additional patient clinical management visits may be scheduled between Q4 week visits as needed when initiating sorafenib treatment, to manage any adverse events and adjustments of sorafenib dosing or to adhere to local standard of care treatment requirements.

	For Patients randomized to TheraSphere, the pre-treatment evaluations and TheraSphere treatment should take place within the first 4 weeks following randomization. After TheraSphere treatment, subsequent study visits will take place at least once every 4 weeks from randomization until progression then every 8 weeks thereafter. Re-treatment of the same patient/tumor with further cycles of TheraSphere is allowed in case of detection during follow-up of a still treatable tumor progression. Patients can receive a subsequent TheraSphere administration in the absence of radiological progression criteria at investigator discretion Patients must meet initial eligibility criteria to receive subsequent treatments. A maximum of three (3) TheraSphere administrations are permitted in total Follow-up visits for response assessment: In both arms, the first follow-up visit will take place at 2 weeks. Thereafter follow-up visits take place at least once every 4 weeks from randomization to week 24 or progression. After week 24, in the absence of progression, follow up visits will occur every 8 weeks from randomization to disease progression and include: 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 QOL questionnaire (FACT-Hep) o Adverse event reporting o Concurrent medication o Abdomen/pelvic CT scan/MRI (every 8 weeks from randomization) o Chest CT scan (every 16 weeks from randomization) o Bone scintigraphy at week 16, every 6 months thereafter Progression for patient management decision-making: For the purposes of this trial, definition of progression for patient management decisions will include assessment of change in PVT status and tumor progression and is defined as: • Radiological progression as defined by RECIST v 1.1 (after receiving all allowable TheraSphere treatments as specified by the protocol) And/Or • Development of extra-hepatic disease beyond the limits defined in the eligibility criteria • Worsening of PVT from baseline defined as change in classification of PVT (per Shi et al) up to Type IIIa; PVT Type IIIb or Type IV may not be treated • ECOG Performance Status ≥2 Follow up visits following progression: In both arms, after Week 24 or after progression has been confirmed and patients have received all treatments allowed under the protocol, study visits will take place once every 8 weeks until death. These visits can be conducted by telephone at the investigator's discretion, if a PS ≥ 2 (symptomatic progression) is assessed and whenever in the best interest of the patient, and will document: o ECOG Performance Status (including date of death if applicable) o Adverse event reporting o Concurrent medication (for treatment of HCC only, recording of medications or therapies used in supportive care is not required).
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.

2 TRIAL SCHEMA



1. Y90 treatment may be planned in one or two sessions and should be started within 4 weeks from randomization

2. A total of no more than 3 sessions of Y90 radioembolization are allowed for each patient

3 SCHEDULE OF EVENTS

3.1 SCHEDULE OF EVENTS: CONTROL ARM

Study Period & Events	Screening	Randomize	Control Arm Treatment & Response Assessment								Progression	Follow up[1]	End of Study
Timing: Study Visits (+/- 7 days) or Events	D -14 to 0[2]	D 0	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W Q8		W Q8	
Informed Consent	x												
Demographics	x												
Medical History	x												
Physical Exam (PE)	x												
Categorization of PVT	x				x		x		x	x			
ECOG Performance Status	x		x	x	x	x	x	x	x	x		x	
Child Pugh Status	x				x		x		x	x			
Medication & Prior Treatment History	x												
Hematology	x			x	x	x	x	x	x				
Coagulation	x			x	x	x	x	x	x				
Chemistry panel, liver function tests	x		x	x	x	x	x	x	x				
Serum Pregnancy[3]	x												
Tumor marker (AFP)	x				x		x		x	x			
Bone Scintigraphy[4]	x						x					(Q6 mo)	
Liver Volume/Tumor mass	x												
Review Eligibility Criteria	x												
Randomize Patient		x											
FACT-Hep questionnaire[5]	x			x	x	x	x	x	x	x		x	
Initiate Sorafenib[6] therapy			x										
Spiral CT of abdomen/pelvis	x[7]				x		x		x	x			
Spiral CT of chest[8]	x[3]						x			x			
Assess/Report Adverse Events	x		x	x	x	x	x	x	x	x		x	x
Review/Record Study Treatment			x	x	x	x	x	x	x	x			
Record Concurrent Medication	x		x	x	x	x	x	x	x	x		x[9]	x
Final Endpoint Efficacy/Safety documentation & exit patient													x

[1] Visits can be conducted by telephone at the investigator's discretion, if a PS ≥ 2 (symptomatic progression) is assessed and whenever in the best interest of the patient

[2] Results from tests and examinations done as part of clinical patient management within 14 days of randomization may be used to satisfy screening requirements to avoid unnecessary duplicative patient testing

[3] Female patients of childbearing potential only

[4] Required for patients with AFP >400 ng/mL to assess metastatic disease at screening, Week 16 then every 6 months

[5] Subjects to complete questionnaire at each study visit; completion not required for telephone follow-up visits

[6] According to sorafenib package insert beginning at Week 2 for Control Arm patients only

[7] Images taken up to 28 days in advance of randomization can be used for baseline images

[8] Imaging to be scheduled every 16 weeks from randomization at alternate Q8 week follow up visits

[9] Document liver treatment medications only; medications used for supportive care do not require documentation

3.2 SCHEDULE OF EVENTS: TREATMENT ARM

Study Period & Events	Screening	Randomize	Treatment Arm Treatment & Response Assessment								Progression	Follow up[1]	End of Study
Timing: Study Visits (+/- 7 days) or Events	D -14 to 0[2]	D 0	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W Q8		W Q8	
Informed Consent	x												
Demographics	x												
Medical History	x												
Physical Exam (PE)	x												
Categorization of PVT	x				x		x		x	x			
ECOG Performance Status	x		x	x	x	x	x	x	x	x		x	
Child Pugh Status	x				x		x		x	x		x	
Medication & Prior Treatment History	x												
Hematology	x			x	x	x	x	x	x				
Coagulation	x			x	x	x	x	x	x				
Chemistry panel, liver function tests	x		x	x	x	x	x	x	x				
Serum Pregnancy[3]	x												
Tumor marker (AFP)	x				x		x		x	x			
Bone Scintigraphy[4] (if AFP >400ng/mL)	x						x					(Q6 mo)	
Liver Volume/Tumor mass	x												
Review Eligibility Criteria	x												
Randomize Patient		x											
FACT-Hep questionnaire[5]	x			x	x	x	x	x	x	x		x	
Hepatic Angiogram[6], TcMAA scan[6], TS Dose Calculation			x										
Order TS			x										
Administer TS treatment[7]				x									
Spiral CT of abdomen/pelvis	x[8]				x		x		x	x			
Spiral CT of chest[9]	X[8]						x			x			
Assess/Report Adverse Events	x		x	x	x	x	x	x	x	x		x	x
Review/Record Study Treatment			x	x								x	
Record Concurrent Medication	x		x	x	x	x	x	x	x	x		x[10]	x
Optional TheraSphere Retreatment[6,11]												x	
Final Endpoint Efficacy/Safety documentation & exit patient													x

[1] Visits can be conducted by telephone at the investigator's discretion, if a PS ≥ 2 (symptomatic progression) is assessed and whenever in the best interest of the patient

[2] Results from tests and examinations done as part of clinical patient management within 14 days of randomization may be used to satisfy screening requirements to avoid unnecessary duplicative patient testing

[3] Female patients of childbearing potential only –can be repeated at physician discretion before repeat TheraSphere treatments

[4] Required for patients with AFP >400 ng/mL to assess metastatic disease at screening, Week 16 then every 6 months

[5] Subjects to complete questionnaire at each study visit; completion not required for telephone follow-up visits

[6] Pre-treatment evaluation is always done before the first TheraSphere treatment and prior to subsequent treatments as needed

[7] TheraSphere must be administered within 4 weeks of randomization

[8] Images taken up to 28 days in advance of randomization can be used for baseline images

[9] Imaging to be scheduled every 16 weeks from randomization at alternate Q8 week follow up visits

[10] Document liver treatment medications only; medications used for supportive care do not require documentation

[11] A maximum of 2 re-treatments with TheraSphere are allowed following hepatic progression for lesions amenable to TheraSphere treatment

4 LIST OF ABBREVIATIONS

AE - Adverse Event

AFP - Alphafetoprotein

ALT – Alanine Transaminase

AST – Aspartate Transaminase

BUN – Blood Urea Nitrogen

CBC – Complete Blood Count

COPD – Chronic Obstructive Pulmonary Disease

CP- Child-Pugh

CRC – Colorectal Cancer

Cr – Chromium

CR – Complete Response

CT – Computed Tomography

CTCAE – Common Toxicity Criteria for Adverse Events

EASL- European Association for the Study of the Liver

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

HBV- Hepatitis B Virus

HCC – Hepatocellular Carcinoma

HCV – Hepatitis C Virus

HDE – Humanitarian Device Exemption

ICF – Informed Consent Form

INR – International Normalized Ratio for prothrombin time

IRB – Institutional Review Board

ITT – Intent–to-Treat

LFT – Liver Function Tests

mRECIST- modified RECIST

MRI – Magnetic Resonance Imaging

NCI – National Cancer Institute

PD – Progressive Disease

PE – Physical Exam

PFS – Progression Free Survival

PLT – Platelet Count

PPP – Per Protocol Population

PR – Partial Response

PRO – Patient Reported Outcome

PS – Performance Status

PT - Prothrombin Time

PTT – Partial Thromboplastin Time

PVT- Portal Vein Thrombosis

PVTT – Portal Vein Tumor Thrombosis

RECIST – Response Evaluation Criteria in Solid Tumor

SAE – Serious Adverse Event

SD – Stable Disease

SOC – Standard of Care

^{99m}TC-MAA – Technetium-99m Magroaggregated Albumin

TEAE – Treatment emergent adverse events

TS – TheraSphere

TTDQoL - Time to deterioration in QoL

TTP – Time-to-Progression

TTSP - Time to symptomatic progression

UADE – Unanticipated Adverse Device Effect

US - Ultrasound

WBC – White Blood Cells

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

Y90-TARE– ^{90}Yttrium trans-arterial radioembolization

5 BACKGROUND AND RATIONALE

5.1 GENERAL DEVICE DESCRIPTION

TheraSphere® consists of insoluble glass microspheres in which yttrium-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 GBq to 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 64.1 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 US package insert is provided in Appendix 1(a).

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 in Russia, India, South Africa, Turkey and Kuwait for the treatment of hepatic neoplasia. The current package insert for Canada is provided in Appendix 1 (b); current Instructions for Use document for Europe is provided in Appendix 1(c).

5.3 RATIONALE FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

According to the American Cancer Society[1], primary liver cancer is a major health problem worldwide. Globally, it is the fifth most commonly diagnosed cancer in men and eighth most common in women, with more than 700,000 new cases in 2007. It is the third leading cause of cancer death in men and sixth among women. Hepatocellular carcinoma is associated with known risk factors[2] including chronic viral hepatitis (types B and C), alcohol intake and aflatoxin exposure, the presence of which vary geographically. In North America and Europe, chronic hepatitis C is a major risk factor while chronic hepatitis B is a major risk factor worldwide.

In 2007, the FDA[3] and EMEA[4] approved sorafenib tosylate (Nexavar® - a registered trademark of Onyx Pharmaceuticals, Inc. and Bayer HealthCare Pharmaceuticals, Inc.), 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[5] trial) in patients with unresectable, biopsy-proven hepatocellular carcinoma. Overall survival was the primary efficacy endpoint. A total of 602 patients recruited primarily from Europe and North America 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 arms. 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). Disease etiology was balanced in both sorafenib and placebo groups: HCV infection (29% vs 27%), alcohol-associated liver disease (26% both arms) and HBV infection (19% vs 18%).

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% CI: 0.55, 0.87), p= 0.00058]. The final analysis of time-to-tumor progression (TTP) by independent radiologic review was based on data from an earlier time point and demonstrated a statistically significant improvement in TTP in the sorafenib arm [median 5.5 vs. 2.8 months; HR: 0.58 (95% CI: 0.45, 0.74), p=0.000007]. In a subset analysis, patients with macrovascular invasion, the hazard ratio for OS favored sorafenib over placebo: HR 0.68 (95% CI 0.49 – 0.93).

To obtain regulatory approval in China a parallel study of sorafenib was undertaken in the Asia-Pacific[6] region, where chronic hepatitis B virus infection is an important etiology factor. In 23 sites in China, Taiwan and Korea, Child Pugh A status patients were randomized in a 2:1 ratio to receive sorafenib (400 mg) or placebo twice daily in 6 week cycles. Of the 271 enrolled patients, 226 were randomized to receive placebo (N=76) or sorafenib (N=150). Demographic and baseline characteristics were similar in both arms as was hepatitis virus status: HBV infection was more common (70.7% sorafenib v.s 77.6% placebo) than HCV infection (10.7% sorafenib vs. 3.9% placebo).

Median overall survival was 6.5 months (95% CI 5.56 – 7.56) with sorafenib compared to 4.2 months (95% CI 3.75 – 5.46) with a hazard ratio of 0.68 (95% CI 0.5 – 0.93)[p=0.014]. Median TTP was 2·8 months (95% CI 2·63—3·58) in the sorafenib group compared with 1·4 months (95% CI 1·35—1·55) in the placebo group (HR 0·57 [95% CI 0·42—0·79]; p=0·0005). Adverse events and efficacy endpoint hazard ratios were consistent with those reported in the SHARP study, indicating similar action of sorafenib in both populations. Subsequent exploratory sub-set analyses[7] in patients with macrovascular invasion and extra hepatic metastases, showed median OS of 5.6 months with sorafenib vs. 4.1 months with placebo; HR 0.75 (95% CI 0.54 – 1.05) and median TTP of 2.7 months with sorafenib vs. 1.3 months placebo; HR 0.58 (95% CI 0.41-0.83).

Sorafenib is now considered the standard of care therapy[8] for patients with advanced HCC, the patients classified as BCLC C according to the Barcelona Clinic Liver Cancer (BCLC) classification system. These authors also suggest using sorafenib as the control arm for randomized clinical trials of first-line systemic agents. Sorafenib is included in the NCCN Clinical Practice Guidelines in Oncology[9] (NCCN– Hepatobiliary cancers V.2.2012 – HCC6) and the EASL-EORTC Clinical Practice Guidelines[2] 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 standard of care 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[4,5] (≥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[10] 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 demonstrated the tolerability of TheraSphere in treatment of patients with HCC and branch PVT[11] and patients with unresectable HCC[12]. Salem et al[13] 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 TTP was 7.9 months (95% confidence interval, 6-10.3). 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) survived 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.

The clinical experience of Salem et al[11,12,13] and a recent meta-analysis of yttrium-90 microsphere radioembolization[14] indicates that TheraSphere is very well tolerated when appropriate patient selection criteria are used. Early reports[15] of serious adverse events possibly associated with the use of TheraSphere, as described in the package labeling documents in Appendix 1, included death, hepatorenal failure, liver abscess, hepatic encephalopathy, hepatic decompensation, radiation hepatitis, radiation pneumonitis, duodenal ulcer, gastrointestinal bleeding and cholecystitis. These more severe events are now uncommon as patients with the high risk factors associated with the occurrence of these events are typically excluded from treatment with TheraSphere. Patients in whom TheraSphere should be used with caution include those with 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.

Recent clinical data in patients with HCC and PVT indicate this group of patients may have a better outcome following TheraSphere treatment as compared to sorafenib treatment. Salem et al[13] indicates that median survival in this group of patients following TheraSphere treatment ranges from 7.7 months (main PVT) to 16.6

months (branch PVT) with an overall average of 10.4 months. A recent paper by Mazzaferro et al[16] reported a median overall survival of 13 months in a cohort of 35 patients with PVT treated with TheraSphere.

6 Study Objectives

The objective of this phase III, prospective randomized trial is to determine whether TheraSphere provides a meaningful benefit in survival in comparison with the standard of care (sorafenib) in patients with good hepatic function and advanced hepatocellular carcinoma (HCC) associated with portal vein thrombosis (PVT).

7 Study Design

This is an open-label prospective, multi-center, randomized, controlled clinical trial that will evaluate the use of TheraSphere compared to standard-of-care sorafenib alone. Up to 25 study centers will participate and recruit patients for the protocol. Participating study sites may be in Europe, Asia or North America. All patients will be followed prospectively from randomization to death.

8 Study Population and Eligibility criteria

Patients diagnosed with unresectable HCC and PVT with adequate liver reserve who are not eligible for any curative procedures may be screened for eligibility criteria.

8.1 Eligibility Criteria

Patients must meet the following eligibility criteria:

1. Patients over 18 years of age, regardless of race or gender
2. Advanced stage HCC confirmed by histology (mandatory in non cirrhotic patients) or non-invasive criteria (EASL/AASLD) with branch PVT.
    - Either naïve or recurrent HCC after curative treatment (minimum 3 months from curative treatment - minor resection or local ablation) is acceptable
    - Branch PVT classified per modified Shi et al 2010[16] as Type I, Type II or Type IIIa (see Section 9.2.5).
3. Unilobar disease which can include multifocal tumors if unilobar and if all nodules (including nodule associated with PVT) are treatable within a single TheraSphere treatment session
4. Tumor volume ≤ 70% of liver volume (determined by visual estimation)
5. Child-Pugh A
6. At least one uni-dimensional HCC target lesion assessable according to the RECIST v1.1 criteria by CT-scan or MRI
7. No confirmed extrahepatic metastases. Patients with indeterminate hepatic hilar lymph nodes up to 2.5 cm in greatest dimension, or with indeterminate lung nodules (single lesion between 1 – 1.5 cm, or multiple smaller lesions with a total diameter ≤ 2 cm) may be included if metastatic disease is deemed unlikely
8. No known contraindications to standard-of-care sorafenib including allergic reaction, pill swallowing difficulty, uncontrolled hypertension or history of cardiac disease (according to sorafenib package insert and country-specific policies, may include evidence of severe or uncontrolled systemic diseases, cardiac arrhythmias (requiring anti-arrhythmic therapy or pace maker), congestive cardiac failure >New York

Heart Association class 2, myocardial infarct within 6 months, prolonged QT/QTc >450ms), 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, renal failure requiring dialysis

9. No evidence of hepatic vein invasion or caval thrombosis
10. Cancer-related symptoms within the ECOG 0-1 category
11. PLT ≥ 50 $x10^3/\mu L$
12. WBC ≥ 1.5 $x10^3/\mu L$
13. AST/ALT ≤ 5 times the upper limit of normal (U/L)
14. Creatinine ≤ 2.0 mg /dL
15. No evidence of pulmonary insufficiency or clinically evident chronic obstructive pulmonary disease.)
16. No indication for any possible curative treatment after multidisciplinary assessment (surgery, ablation, transplantation)
17. No previous treatment with Sorafenib for more than 4 weeks during the 2 previous months; no prior sorafenib-related toxicity at any dose and/or duration defined as documented sorafenib-related grade 3 or 4 adverse events that led to sorafenib discontinuation
18. No initiation of any other anti-tumor therapy including chemotherapy, radioembolization (maximum lung shunt of 20% for prior radioembolization) or investigational drug treatment within 30 days before the beginning of the study
19. In case of patients progressing from an intermediate to an advance stage because of occurrence of PVT, enrolment is allowed if previous conventional or drug eluting TACE was performed at least 3 months prior to screening phase
20. Patients cannot be on a liver transplantation list
21. No history of organ allograft
22. No contraindication to angiography or selective visceral catheterization
23. No history of severe allergy or intolerance to contrast agents, narcotics, sedatives or atropine that cannot be managed medically
24. No previous external beam radiation treatment to the liver
25. No evidence of continuing adverse effect of prior therapy
26. No active GI bleeding and any bleeding diathesis or coagulopathy that is not correctable by usual therapy or hemostatic agents (e.g., closure device)
27. No evidence of any disease or condition that would place the patient at undue risk and preclude safe use of microspheres (TheraSphere®) treatment
28. Negative serum pregnancy test in females of child-bearing potential; patients who are breast-feeding cannot participate in this trial
29. Life expectancy of greater than 3 months
30. No participation in concurrent interventional clinical trials
31. Signed informed consent

9 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. All study visits that take place after the screening/randomization period should occur within +/- 7 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 prior to signing of the informed consent may be used for screening and baseline evaluations providing these scans were taken within 28 days before randomization and conform to the protocol image specifications in Section 9.2.17. External imaging will be accepted as long as performed with the necessary specifications, digitalized, and retrievable from internal radiological archive system. The quality of external imaging has to be adequate in order to capture liver volume measurement and mass calculations required at baseline. Test results obtained for clinical patient management and before signing of informed consent do not need to be repeated and may be used for screening assessment provided tests were conducted within 14 days of randomization. The date of screening is the date all screening procedures are completed.

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 9.2.1.
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. Categorization of type of PVT as described in Section 9.2.5 will be done.
6. ECOG Performance Status will be assessed as described in Section 9.2.6.
7. Child Pugh will be assessed as described in Section 9.2.7.
8. Medication history & Prior treatment history will be obtained as described in Section 9.2.8.
9. The liver tumor volume calculation will be completed as described in Section 9.2.9.
10. Baseline clinical laboratory tests, blood chemistry, hematology and coagulation, as described in Section 9.2.10 will be done.
11. A serum pregnancy test as described in Section 9.2.11 will be administered for all female patients of childbearing potential.
12. The patient's eligibility to participate will be assessed as described in Section 9.2.12.
13. A baseline AFP level will be drawn as described in Section 9.2.13.
14. Baseline images for efficacy evaluation (Spiral CT of abdomen/pelvis and Spiral CT of chest) will be taken as described in Section 9.2.17. Images taken within 28 days prior to randomization may be used as baseline images.
15. Baseline Patient Reported Outcome assessments will be made as described in Section 9.2.14.
16. Bone scintigraphy as described in Section 9.2.17.

Following Screening, patients meeting the eligibility criteria will be randomized as described in Section 9.2.15.

9.1.2 Patients randomized to the Control Arm

9.1.2.1 Week 2 following Randomization

The following study-related activities will be completed as appropriate. Patients may need several visits during this period to adjust the dose of sorafenib.

1. Initiate sorafenib treatment as described in Section 9.2.16.2.
2. Record details on the clinical assessments and administration of sorafenib.

3. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.3.

9.1.2.2 Q4 Weeks Following Randomization to Progression

Additional clinical management visits are permitted to meet local standard of care treatment requirements. In addition to the administration of sorafenib and the evaluations associated with that therapy, at every 4 week visit following randomization to week 24 or progression the following activities will be completed. In the absence of progression after 24 weeks the follow up visit schedule will change to every 8 weeks from randomization until determination of progression for the purposes of clinical management (Section 9.2.20).

1. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.3.
2. ECOG Performance Status will be assessed as described in Section 9.2.6
3. Clinical laboratory tests, blood chemistry, hematology and coagulation, AFP, as described in Section 9.2.10 will be done.
4. Patient Reported Outcome assessments will be obtained as described in Section 9.2.14.

9.1.2.3 Q8 Weeks Following Randomization to Progression

1. CT/MR images will be taken as described in Section 9.2.17 for efficacy assessment
2. Chest CT/MRI images will be taken every 16 weeks as described in Section 9.2.17.
3. Bone scintigraphy for selected patients at week 16 then every 6 months thereafter as described in Section 9.2.17

9.1.2.4 Q8 Weeks Following Progression to Death

Every 8 weeks following determination of progression (Section 9.2.20), until death, a clinic visit or telephone follow-up (at the investigator's discretion, if a PS ≥ 2 (symptomatic progression) is assessed and whenever in the best interest of the patient) will be conducted. The following activities will take place:

1. ECOG Performance Status (including date of death, if applicable) will be assessed as described in Section 9.2.6.
2. Record any treatment and concurrent medications to treat hepatocellular carcinoma and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.3. Medications and therapies used in supportive care will not be recorded.
3. Patient Reported Outcome assessments will be obtained as described in Section 9.2.14 at clinic visits only.
4. Child Pugh status will be assessed as described in Section 9.2.7

9.1.3 Patients randomized to the Treatment Arm

9.1.3.1 Weeks 1-4 following Randomization

The following study-related activities will be completed:

1. Complete appropriate clinical laboratory tests, including AFP, as described in Section 9.2.10 within 7 days prior to TheraSphere administration.
2. Conduct pre-TheraSphere evaluation within Week 2, as described in Section 9.2.16.1.2, and administer TheraSphere by the end of Week 4 to patients able to receive TheraSphere treatment as described in Section 9.2.16.1.7. For patients who are determined to be not treatable with

TheraSphere following the pretreatment evaluation, patients may begin sorafenib therapy as soon as possible.
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 12.3.

9.1.3.2 THERASPHERE RE-TREATMENT

Patients can receive a subsequent TheraSphere administration in the absence of radiological progression criteria at investigator discretion Patients must meet initial eligibility criteria to receive subsequent treatments. A maximum of three (3) TheraSphere administrations are permitted in total. TheraSphere treatments may be administered after hepatic progression if the lesions are amenable to treatment. Any re-treatment should take place at least 28 days from the last TheraSphere treatment. These optional treatments are not required protocol treatments and are administered at the discretion of the investigator. The following activities will take place:

1. Complete appropriate clinical laboratory tests, as described in Section 9.2.10.
2. Conduct pre-TheraSphere evaluation as with interventions as indicated and administer TheraSphere as described in Sections 9.2.16.1.2 and 9.2.16.1.7.
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 12.3.
5. Record Child Pugh status as described in Section 9.2.7

9.1.3.3 Q4 WEEKS FOLLOWING RANDOMIZATION TO PROGRESSION

Additional clinical management visits are permitted to meet local standard of care treatment requirements. At every 4 week visit following randomization to week 24 or progression, the following activities will be completed. In the absence of progression after 24 weeks the follow up visit schedule will change to every 8 weeks from randomization until determination of progression for the purposes of clinical management (Section 9.2.20).

1. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.3.
2. ECOG Performance Status will be assessed as described in Section 9.2.6.
3. Clinical laboratory tests, blood chemistry, hematology and coagulation, AFP as described in Section 9.2.10 will be done.
4. Patient Reported Outcome assessments will be obtained as described in Section 9.2.14.

9.1.3.4 Q8 WEEKS FOLLOWING RANDOMIZATION

1. CT/MR images will be taken (as described in Section 9.2.17 for efficacy assessment).
2. Chest CT/MRI images will be taken every 16 weeks as described in Section 9.2.17.
3. Bone scintigraphy for selected patients at week 16 then every 6 months thereafter as described in Section 9.2.17
4. Record Child Pugh status as described in Section 9.2.7

9.1.3.5 Q8 WEEKS FOLLOWING PROGRESSION TO DEATH

Every 8 weeks following determination of progression (Section 9.2.20), until death, a clinic visit or telephone follow-up (at the investigator's discretion, if a PS ≥2 (symptomatic progression) is assessed and whenever in the best interest of the patient) will be conducted. The following activities will take place:

1. ECOG Performance Status (including date of death, if applicable) will be assessed as described in Section 9.2.6.
2. Record any treatment and concurrent medications to treat hepatocellular carcinoma and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.3. Medications and therapies used in supportive care will not be recorded.
3. Patient Reported Outcome assessments will be obtained as described in Section 9.2.14 at clinic visits only.

For patients undergoing retreatment procedures, study visits will occur Q8 weeks, until determination of subsequent hepatic progression, during which the procedures described in Sections 9.1.3.3 and 9.1.3.4 will be completed.

9.1.4 Patient Completion or Early Withdrawal

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

1. Record the date and reason for study exit, as described in section 9.2.20.
2. Record the ECOG status as described in Section 9.2.6, as appropriate.
3. Complete, as appropriate, any clinical laboratory tests, including AFP, as described in Section 9.2.10.
4. Record any treatment and concurrent medications and any adverse events as described in Sections 9.2.18, 9.2.19 and 12.3.
5. Complete any CT/MR images, as appropriate, for efficacy assessment.
6. Complete the Patient Reported Outcome assessments, as appropriate, as described in Section 9.2.14.

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/EC 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 (date of birth, 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 (e.g. 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, sexual reproductive function, vascular).

The diagnoses and history of HCC will be recorded separately from other medical history.

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), and temperature (T)
- Height and weight
- Chest, abdomen
- Heart
- Extremities
- Brief neurological examination (level of consciousness, orientation, sensation, and motor function)

9.2.5 Classification of PVT

The reference standard for characterizing PVT in cirrhotic patients with or without HCC is a histopathologic examination. However in the present trial for practical reasons, contrast enhanced CT scan or MRI and clinical and laboratory findings can be relied on for categorization of PVT adapted from Shi et al 2010[17] (see Appendix 2). Portal vein tumor thrombosis (PVTT) in HCC is defined as expansion of the thrombosis within the involved portal vein adjacent to the primary tumor and enhancement of the thrombus itself during the arterial phase on contrast enhanced CT or MRI.[18,19]

The mandatory requirements qualifying patients for the present study is the confirmation, according to standard criteria (histology or EASL/AASLD guidelines) of advanced stage HCC associated with branch PVT. For the purpose of this study, branch PVT is defined as Type Ia or Ib, Type IIa or IIb or Type IIIa as noted below. Presence of PVT in absence of focal liver lesions or associated only with high levels of AFP, is not eligible for the study because of the lack of a target lesion.

At the screening visit and subsequent Q8 weekly visits:

- venous location of the PVT will be recorded on the eCRF
- tumor location (lobe/segment) will be recorded on the eCRF
- PVT will be categorized based on dynamic imaging studies as:
  - Type I: segmental, to be demonstrated at imaging in at least one of the eight segmental branches of the portal vein (peripheral or sub-segmental venous invasion are not eligible)
  - Type II: branched (left or right branches of the portal vein)
  - Type III has been modified on the basis of extension of the tumor thrombus rather than on the length of the tumor thrombus; in particular:
    - Type IIIa, eligible to the study: thrombus involving the main portal trunk although allowing blood flow to the contralateral lobe (with no thrombosis)
    - Type IIIb, NOT eligible to the study: thrombus in the main portal trunk occluding blood flow to the contralateral lobe; includes portal cavernomas associated with main trunk thrombosis
  - Type IV: main PVT – NOT eligible to the study; extended (mesenteric or splenic veins and/or sovra-hepatic veins)

9.2.6 ECOG Performance Status

Performance Status will be assessed according to the Eastern Cooperative Oncology Group[20] performance status characteristic (see Appendix 3).

9.2.7 Child Pugh 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 week visit.

9.2.8 Medication and Prior Treatment History

The use of concurrent medications (medications taken within 30 days of screening and during the conduct of the study) will be obtained and documented on the relevant eCRF.

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.

9.2.9 Liver Tumor Volume Determination

Triple Phase CT is the fastest and most reproducible method of capturing liver volume measurement and mass calculations required at Baseline. Triple phase CT will be used in accordance with site standards for dosimetry determination. In addition CT or MRI baseline images should be taken for determination of progression. Subsequent images to determine efficacy outcomes must be taken using the same modality and settings used for the baseline image. 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 lobar and tumor volumes determined. Tumor replacement, expressed as a per cent of total liver volume, will be recorded on the relevant eCRF.

9.2.10 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.

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

9.2.11 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.

9.2.12 Review Eligibility Criteria

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

9.2.13 HCC Tumor Biomarker (AFP)

Blood will be collected prior to and at the Q8 weeks study follow-up visits following randomization to determine the baseline and subsequent AFP values.

9.2.14 Patient Reported Outcome

Functional Assessment of cancer Therapy – Hepatobiliary Questionnaire (FACT-HEP) Patient Reported Outcome instrument suitable for patients being treated for hepatocellular carcinoma will be administered at study visits throughout the trial (every 4 weeks to Week 24 or progression, whichever is earliest), then every 8 weeks thereafter. The baseline Quality of Life (QOL) FACT-HEP assessments will be obtained during the Screening period after the Informed Consent is signed and before the first treatment in either arm is administered. If the patient cannot attend follow-up visits, FACT-HEP questionnaires will not be completed.

.

9.2.15 Randomization (Day 0)

According to an intention-to-treat (ITT) methodology, randomization will be performed upfront, before any further invasive tumor assessment (angiogram) or treatment planning.

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

If a patient is determined to be eligible to participate in the trial, the study site will contact the central randomization office via telephone or by internet 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 site number (e.g. 01) and a patient identifier number (e.g. 001).

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

- AFP ≤ 400 ng/mL or >400 ng/mL
- Participating trial site

Although this will not be considered as stratification criteria upfront, each patient will be registered as naïve or recurrent, i.e. whether or not the HCC diagnosis presents at first diagnosis, with no previous treatment, or as a recurrent tumor.

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

Patients who do not meet the eligibility criteria should not be randomized and the reason for treatment ineligibility should be documented on the Screen Failure Log.

9.2.16 Study Treatments

9.2.16.1 TheraSphere

TheraSphere will be administered to all disease present at randomization.

9.2.16.1.1 Re-treatment

Patients can receive a subsequent TheraSphere administration in the absence of radiological progression criteria at investigator discretion. During follow-up, for patients in the Treatment arm who have demonstrated hepatic progression with hepatic lesions amenable to TheraSphere., re-treatment with TheraSphere is allowed. Any re-treatment should take place at least 28 days from the last TheraSphere treatment.

Patients must meet initial eligibility criteria for TheraSphere treatment (Section 8.1) to receive subsequent treatments. A maximum of three (3) TheraSphere administrations are permitted in total.

Patients will undergo additional pre-treatment evaluations as described in Section 9.2.16.1.2 at the investigator's discretion prior to administration of subsequent TheraSphere treatments to assess and address any changes in extra-hepatic shunting that may have developed.

9.2.16.1.2 TheraSphere Pre-Treatment Evaluation

Patients randomized to the Treatment arm must undergo the following evaluations to determine eligibility to receive the TheraSphere. These 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 (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.

TheraSphere should not be administered to a patient randomized to the Treatment arm 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 that cannot be corrected by dose reduction of TheraSphere.

In the event that a patient randomized to the TheraSphere arm is determined not to be suitable for and/or cannot be safely treated with TheraSphere, that patient will not receive TheraSphere and may proceed to treatment with SOC sorafenib regimen as described in Section 9.2.16.2.

9.2.16.1.3 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. 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 Y90 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[21]. 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 3 or more infusions are administered. The volume that needs to be used for Y90 dosimetry is that volume of liver that is perfused by the vessel that will be infused.

Arterial redistribution techniques are permitted for intra-tumoral and/or less than one liver segment.

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,c]	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)

9.2.16.1.4 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. Patients will receive TheraSphere at a dose consistent with the approved product label. The target dose is 120 Gy ± 10%. Dose reduction is permitted when required to ensure radiation exposure to the lung is less than 30 Gy for a single treatment or 50 Gy cumulative. Dose reduction below 80 Gy per treatment is not permitted.

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: Convert the target liver volume to mass assuming a conversion factor of 1.03g/cm^3.

Calculation of Activity required to deliver a desired dose of 120 Gy:
The amount of radioactivity required to deliver a 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:

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

Calculation of estimated lung radiation exposure (Gy):

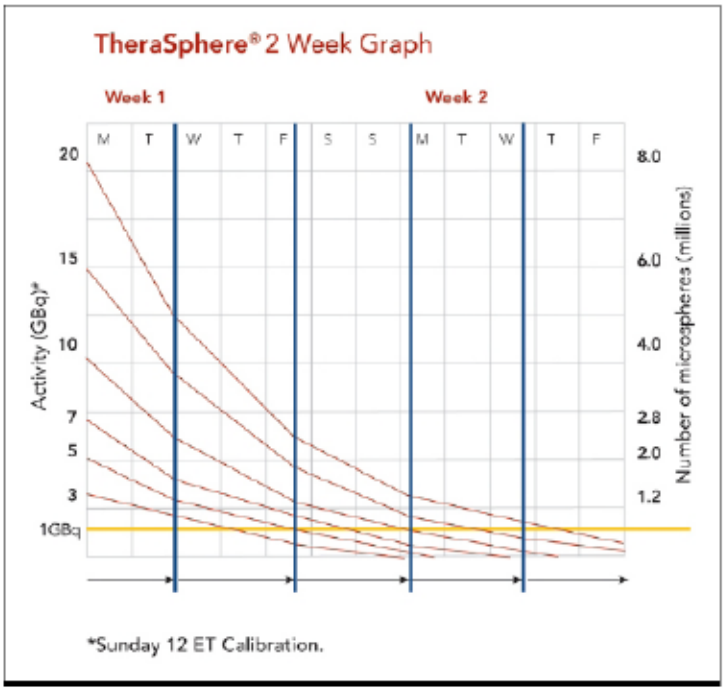
Lung Dose (Gy) per infusion = 50 * Calculated Activity in gigabecquerel (GBq) * F

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

9.2.16.1.5 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.



Note: The number of microspheres does not change over time.

9.2.16.1.6 THERASPHERE ORDERING

Orders must be placed using the order form provided by the sponsor. Standard dose vial sizes (3 GBq, 5 GBq, 7 GBq, 10 GBq, 15 GBq and 20 GBq) are made to stock and can be ordered at anytime. Orders for custom size dose vials must be received at TheraSphere Customer Service 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.

9.2.16.1.7 THERASPHERE ADMINISTRATION

TheraSphere will be administered at a dose consistent with the approved product label. A target dose of 120 ± 10% Gy to the target liver tissue is recommended. Dose reduction to a minimum dose of 80 ± 10% Gy is permitted to manage radiation exposure to the lungs within the limits of 30 Gy for a single infusion and 50 Gy cumulative.

During follow-up, for patients in the Treatment arm who have demonstrated hepatic progression with hepatic lesions amenable to TheraSphere, re-treatment with TheraSphere is allowed.

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 North America. It is generally considered to be an inpatient procedure in some countries 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 or proton pump inhibitor) 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.

9.2.16.1.8 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 arm must certify continued eligibility prior to administration of TheraSphere. A new blood draw for labs and pregnancy and an ECOG Performance Status test may be performed within 7 days before TheraSphere administration at physician discretion to confirm baseline results.

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 activity fraction

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

$$R = (W-b')/(I-b)$$

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) and adjusted for radioactive decay to the time of waste measurement
b' = background dose rate prior to waste measurement
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:

$$\text{Lung dose (Gy)} = 50^* \text{ activity delivered (GBq)}^*F$$

9.2.16.1.9 TheraSphere Post-Treatment Patient Management

Immediately following treatment, the patient should remain under observation consistent with institutional standard of care 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 or proton pump inhibitor) 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 immediate post-treatment period may be administered according to institutional standard of clinical care and should be documented on the Concurrent Medications eCRF.

9.2.16.1.10 Radiation Safety in the Immediate Post-Treatment Period

Special radiation isolation procedures for Treatment arm 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[22]. The predominant byproducts 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.

9.2.16.2 SOC SORAFENIB TREATMENT

Control arm patients will start SOC sorafenib therapy within 2 weeks after randomization.

All patients in the Control group will receive SOC treatment with sorafenib in accordance with the package insert. In accordance with the sorafenib package insert and country-specific policies, 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). In the United Kingdom, 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 as SOC monitoring.

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. In those countries where monitoring by ECG is required, 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 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

9.2.16.3 POST-PROGRESSION TREATMENT:BEST AVAILABLE CARE

All patients who meet the criteria for progression specified in Section 9.2.20 and received the treatments as described for either arm of the trial can receive institutional best available care. Patients in the control arm

who have progressed are not allowed to cross-over to the treatment arm. Best available care is based on physician judgment and current standard of care practices, including sorafenib.

For patients in the control arm: In the case of recurrent unifocal lesion, resection or radiofrequency ablation are allowed providing the lesion(s) treated with sorafenib demonstrates tumor response (PR or CR) by RECIST v1.1. For any other progression, if resection or ablation is not appropriate, patients may receive best available care.

For patients in the treatment arm: In case of a previously treated tumor with progression per RECIST v 1.1 detected during follow up evaluations, re-treatment with TheraSphere is allowed if it does not exceed the maximum allowable three Y90 treatments. In the case of a treatable multifocal progression (ipsi or contralateral), a Y90 re-treatment is allowed if the lesion(s) treated with TheraSphere demonstrate tumor response (PR or CR) by RECIST v1.1, the lesion is amenable to TheraSphere treatment and the re-treatment procedure does not exceed the permited maximum three treatments.

9.2.17 Efficacy Imaging – CT/MRI

Baseline efficacy imaging scans will be obtained during screening and efficacy assessment scans will be taken every 8 weeks post randomization until progression is confirmed (see Section 9.2.20). 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. Triple phase CT will be used in accordance with site standards at baseline for dosimetry determination. SPECT imaging may be performed according to standard of care practices for clinical management but is not a study requirement.

Spiral CT abdomen/pelvis – 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.

Spiral CT Chest – 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.

To enable analysis of secondary study endpoints using radiological assessment, investigators will identify, read and use bidimensional measurements of target lesions for size and will record evidence of enhancement and increase in dimension of a pre-existing thrombus for all image timepoints. These data will be captured on the eCRF. Comparison between baseline and subsequent images of quantitative and qualitative findings will determine response according to RECIST v 1.1[23], mRECIST[24] and EASL which are assessed separately in secondary endpoint analyses.

Bone Scintigraphy – Bone scintigraphy to assess spread of metastatic disease will be performed according to institutional standards. For patients with AFP > 400 ng/mL at screening, results of bone scintigraphy will be recorded at the screening visit and subsequent study visits according to the site standard practice (week 16 study visit and 6 months thereafter (i.e. months 10, 16, 22, etc.)). Bone scintigraphy is suggested whenever there is an unjustified increase in AFP or the patient experiences bone pain or symptomatic deterioration and repeated at a frequency according to site standard practice.

9.2.18 Study Treatment Medication Record

The administration of study treatment 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 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.

Following determination of progression and receipt of treatment options in either arm of the study, record only medications used specifically for the treatment of HCC. Other medications do not need to be recorded.

9.2.20 Definition of Progression For Patient management Decision-Making

For the purposes of this trial, definition of clinical progression for patient management decisions will include assessment of change in PVT status and tumor progression and is defined as:

- Radiological progression as defined by RECIST v 1.1 (after receiving all allowable TheraSphere treatments as specified by the protocol)
  And/OR
- Development of extra-hepatic disease beyond the limits defined in the eligibility criteria
- Worsening of PVT from baseline defined as change in classification of PVT (per Shi et al) up to Type IIIa; Type IIIb or Type IV may not be retreated
- ECOG Performance Status ≥2

9.2.21 Study completion

Patients complete the trial upon reaching the primary efficacy endpoint of death.

9.2.22 Patient Withdrawal

A patient may 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 withdrawal include:

- Death of the patient
- Patient's desire for any reason to withdraw consent
- Administrative reasons (e.g. study termination)
- 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 the patient is removed due to pregnancy or because of intolerance to the study treatment, he/she should be under medical supervision for as long as deemed appropriate by the treating physician. If the patient 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.

10 Statistics

10.1 Sample Size Estimate

This is a randomized open label multi-center Phase III adaptive trial using a group sequential design with a primary end-point of OS.

The study is designed to detect a 4 months increase in median OS time from 9 months in the control arm to 13 months in the TheraSphere arm (i.e., hazard ratio = 0.69), using a log rank test.

A maximum of 250 deaths will yield 80% power to detect the target difference in median OS (i.e., HR = 0.69) 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[25]). It is estimated that a maximum of 320 patients will need to be recruited over 42 months, with a 1 year 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.

Sample size modification will be considered at the second interim analysis using the approach described in Mehta and Pocock[26] (2011), which employs an un-weighted test statistic at the final analysis as recommended by Burman and Sonneson[27] (2006). If the sample size is increased after the second interim analysis, the final analysis is planned when approximately, but no less than, 430 deaths have occurred, which will result in 80% power to detect an improvement in median OS from 9 to 12 months using a log rank test with a final two-sided alpha of 0.0322. It is estimated that approximately 500 patients will need to be recruited over 72 months, with a 1 year additional follow-up period, in order to observe 430 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.

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-Arms

- **Intent to Treat population**

- All randomized patients will be analyzed according to the treatment group to which they are assigned.

- **Per Protocol Population (PPP)**

All randomized patients will be analyzed according to the treatment actually received and adherence to the protocol. Patients who are determined to have major protocol violations as defined in Section 14 will be excluded from the PPP analysis

- **Safety Analysis Population (SAP)**

All randomized patients who received study treatments at least once will be analyzed according to the treatment actually received.

10.2.2 Trial Endpoints

10.2.2.1 PRIMARY EFFICACY ENDPOINT

The primary study endpoint is overall survival (OS) time, 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 treatment and control arms from time of randomization to radiological progression (including new liver lesions and extra-hepatic lesions) according to RECIST v 1.1, modified RECIST and EASL criteria (see Appendix 5), assessed separately by investigator determination.

Time-to-symptomatic-progression will be compared between treatment and control arms from randomization to symptomatic progression. Symptomatic progression is defined as clinical progression to ECOG performance status ≥2. Such deterioration in PS should be observed at one subsequent evaluation 8 weeks later.

Tumor Response according to RECIST v 1.1, modified RECIST and EASL response criteria based on investigator assessment. At Baseline, target tumors are identified, and quantitative and qualitative (enhancement, necrosis) characteristics recorded. At all subsequent follow-up visits, the images (using the same modality) for the same target lesions will be read, and quantitative and qualitative characteristics recorded. Comparing these findings for follow up visits to the baseline findings, tumor response according to RECIST v1.1, modified RECIST or EASL criteria will be determined under separate analyses. Appendix 5 provides a summary of these criteria.

Patient Reported Outcome Assessments (including 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).

10.2.3 EFFICACY ANALYSIS

The efficacy analyses will be performed on the ITT and PPP populations.

10.2.3.1 PRIMARY ENDPOINT STATISTICAL ANALYSIS PLAN

The Kaplan-Meier method will be used to estimate the OS curves in the two treatment arms; 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, 125 deaths, with a two-sided p-value ≤0.0177 allowing the study to be stopped early for efficacy. A second interim analysis is planned at approximately, but no less than, 188 deaths, with a two-sided p-value ≤0.0228 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[28] (2006).

Sample size modification will be considered at the second interim analysis using the approach described in Mehta and Pocock (2011). The exact criteria to allow sample size modification will be provided in the IDMC charter.

Final Analysis: The final analysis, without a sample size modification, is planned when approximately, but no less than, 250 deaths have occurred. A two-sided p-value ≤0.0322 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, 430 deaths have occurred, which will result in 80% power to detect an improvement in median OS from 9 to 12 months using a log rank test with a final two-sided alpha of 0.0322.

10.2.3.2 SECONDARY ENDPOINT STATISTICAL ANALYSIS PLAN

For secondary efficacy endpoints, each comparison between treatment groups will be conducted at the final analysis with 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.

- Time to progression (TTP) will be calculated as the interval between the randomization date and the date of first disease progression as defined by the respective criteria noted below, 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 arms; comparison between the curves will be performed using the log-rank test. Median TTP will be reported. Progression will be assessed separately using:
  - RECIST v1.1 criteria
  - mRECIST criteria
  - EASL response criteria (assessed bidimensionally on enhancing tissue)
- Time to symptomatic progression (TTSP) will be calculated as the interval between the randomization date and symptomatic progression, defined as assessment of ECOG performance status ≥2 with or without tumor progression based on imaging. Deterioration in performance status is to be observed at one subsequent evaluation 8 weeks later. For subjects who had not progressed symptomatically at the time of analysis, TTSP will be censored at their last date of PS assessment. 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.Median TTSP will be reported.
- Tumor response rate. The response probability will be estimated in each of the two treatment arms as proportion of CR+PR over the total number of ITT or PPP patients. The disease control rate (ie, CR+PR+SD) will also be compared between the treatment arms. The minimum time between image acquisitions is 6-8 weeks. Tumor response rate will be assessed separately using:
  - RECIST v 1.1
  - mRECIST
  - EASL

  Tumor response will be compared using the continuity adjusted Newcombe-Wilson test, and the 95% confidence limits will be calculated

- Patient reported outcome (PRO). The total score 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 arm. The two treatment arms will be compared applying a mixed linear model with the treatment as factors, the baseline score and the relative time from baseline as covariates. 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 and will be compared using a log-rank test.

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

10.2.4 Safety Analysis

The safety analyses will be performed on the SAP 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 the MedDRA coded primary system-organ class (SOC) and preferred term.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.

10.2.5 Other Analyses

The number of randomized patients, the number of patients treated, the number of patients in each analysis population will be summarized. Also 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 PPP 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.

Multi-variate Cox regression analysis of time-to-event efficacy endpoints will be conducted on AFP level, age, gender, naïve or recurrent disease, HCC diagnosis present at first oncology diagnosis, prior treatment, geography to determine the impact of these factors on trial endpoints.

As a sensitivity analysis, to address the poolability of data across regions (ie, Europe, North America or Asia), 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. The specific

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

AFP levels at Q8 week visits for patients with AFP >400ng/mL at screening will be compared, in separate analyses, to RECIST v 1.1, mRECIST and EASL response criteria to correlate biological and radiological response to explore the use of variations in AFP as a confirmation of radiological response.

Analyses of all primary and secondary endpoints will be performed in a descriptive manner only using the following subgroups:

- Right vs left vs both branch PVT
- Ipsilateral vs contralateral tumor/PVT location

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 14155:11:4.9. The IDMC will meet periodically during the study to review enrollment, protocol deviations, and safety events for the study. In addition the IDMC 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 and will make formal recommendations to the study Sponsor 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.

11 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 Adverse Events

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

12.1 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.

12.2 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 if 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.

12.3 Recording Adverse Events

All adverse events and adverse device effects will be documented from the date of informed consent until study exit for randomized patients.

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. AEs ongoing at study exit will be followed to resolution. 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.

12.3.1 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.

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 Arm.

12.4 Submitting Expedited Safety Reports

Any SAE, SADE or UADE (defined previously) must be reported by telephone or fax to Biocompatibles or its 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 by 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/EC of all unexpected SAE or UADE. These events will be reported by the sponsor as appropriate to the regulatory authorities according to relevant jurisdictional 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.

12.5 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 the initiation of trial treatment, 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/EC.

12.6 Expected Adverse Events

12.6.1 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 sequellae; constipation, heartburn, weight loss, fever, ascites, muscle weakness, variations in hemoglobin, neutrophils and leukocytes, GI ulcer, dyspnea, arrhythmia, diarrhea, liver dysfunction, hypotension, insomia, 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.

12.6.2 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 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 that may be located in Europe, Asia or North America.

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/EC and clinical protocol review process in compliance with the appropriate regulations (21 CFR 56 or ISO 14155:11:3) 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 Biocompatibles. Generally, an adequate level of experience consists of a minimum of 5 TheraSphere administrations for sites without

radioembolization experienceand at least 3 administrations of TheraSphere for sites experienced in radioembolization with a 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) or Ethics Committee (EC) has reviewed and approved the protocol and the Informed Consent Form (ICF).

The final IRB/EC approved protocol, consent form, documentation of IRB/EC 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 to the institution's IRB/EC.

- 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 any protocol treatment.
- Recruitment and advertising materials must have written IRB/EC approval before use.
- The Investigator is responsible for obtaining and maintaining IRB/EC approval at his facility and providing copies of all IRB/EC 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 (with the exception of Final Report) must be obtained before study enrollment can begin. Additionally, in European or Asian Countries, all those documents required as per ICH/GCP and local laws for site activation need to be obtained/provided to Biocompatibles or its designee before the enrolment can begin at sites.

- Institutional Review Board/Ethics Committee 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/EC 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/EC for all subsequent protocol amendments and changes to the ICF. The investigator should notify the IRB/EC of deviations from the protocol and SAEs as required by local procedures.

The investigator will be responsible for updating the IRB/EC 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/EC 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/Ethics Committee Membership Roster

As required in accordance with jurisdiction regulations, the investigator must submit a complete and current roster of the IRB/EC to the sponsor (Biocompatibles) or designee. Some institutions, on grounds of confidentiality, may not release the IRB/EC roster. In such instances, the institution's General Assurance Number, assigned by the United States 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 Biocompatibles. A copy of this form will be given to the investigator for their files. The original form will be maintained by Biocompatibles.

- Curriculum Vitae

The investigator will provide Biocompatibles or designee with his/her up-to-date curriculum vitae and those of any sub-investigators or staff personnel with significant trial responsibilities.

- Laboratory Certification and Normal Values

The Investigator will provide Biocompatibles 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 Biocompatibles 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 14155:11:9.2). The investigator is responsible for ensuring completed and signed financial disclosure forms, which are provided by Biocompatibles 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 Biocompatibles 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/EC 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 or national 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 purposes of this study the minimum retention for Study Documentation is a period of two (2) years after the date on which the Study is terminated or completed.

Completed eCRFs that are dated and signed by the investigator must be made available for review and retrieval by Biocompatibles or designee at the time the subject completes the study. Biocompatibles 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 Biocompatibles, as well as representatives of a regulatory agency (e.g. the Food and Drug Administration) or the institutional review board/ethics committee (IRB/EC), have access to source documents (i.e. 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. Biocompatibles reserves the right to terminate the study at any site 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 US 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 Biocompatibles and the IRB/EC as required by the policies of the IRB/EC.

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 Biocompatibles, or the appropriate regulatory authority, or designate representing these organizations.

13.7 INFORMED CONSENT

An IRB/EC 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 14155:11:3.7 or equivalent, as appropriate to his/her country. The Investigator will ensure that the local IRB/EC 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 patients 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/EC. The Investigator will provide Biocompatibles a copy of the IRB/EC 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 study termination.

13.9 Patient Privacy and Confidentiality

All collected patient data will be treated confidentially and identified only by a patient identification number and patient initials (where allowed). 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, Biocompatibles (the Sponsor) or its agents, and the Data Safety Monitoring Board 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 Biocompatibles and/or a representative of the appropriate regulatory agency and the Data Safety Monitoring Board. 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 Country-specific guidelines and laws, in ISO 14155:11 and in Section 11 of the US 21 CFR 812.100, 812.110 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 Biocompatibles to monitor the trial at appropriate and convenient intervals and provide an adequate, secure area, within the study site facility for a Biocompatibles representative to conduct these monitoring activities.

14 Protocol Deviations

It is vital to the success of the study that the investigator adheres to the details of the protocol. All deviations from the protocol must be approved by the sponsor before implementation.

Protocol deviations will be tracked according to the following categories:

1. Informed Consent process not followed
2. Screening tests or procedures out of window or not done
3. Imaging tests not performed as required
4. Inclusion/Exclusion criteria violation
5. TheraSphere dose delivery outside range of 80 to 150 Gy
6. Lung dose exceeds 30 Gy single treatment, 50 Gy cumulative
7. Study visits , tests or procedures conducted out of window or not done
8. Liver-directed treatment of HCC other than TheraSphere

15 Protocol Violations

Major protocol violations are defined as:

- Enrollment Violations:
  - Eligibility criteria deviations
  - No informed consent

- Post-Treatment Violations:
  - Administration of liver-directed local regional therapy other than that specified in the protocol following intra-hepatic progression
  - Patients with disease progression who have tumor response data missing for 2 follow-up visits prior to progression.

16 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 conduct remote monitoring and 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 Study Termination

Biocompatibles reserves the right to discontinue this study for administrative reasons at any time. The End of Trial is defined as database hard lock.

The manuscript reporting the outcome of this trial will be authored by the Principal Investigators with input from investigators and submitted to a peer-reviewed scientific journal for publication.

APPENDICES

1. TheraSphere Product Labeling
    a. US Package Insert
    http://www.therasphere.com/physicians-package-insert/package-insert-us.pdfp
    b. CA Package Insert
    http://www.therasphere.com/physicians-package-insert/package-insert-ca.pdf
    c. EU Instructions for Use
    http://www.therasphere.com/physicians-package-insert/package-insert-eu-en.pdfp (other languages are available at this website

2. PVT Classification: Table 1 and Figure 1 adapted from *Shi J et al., Ann Surg Oncol 2010.*

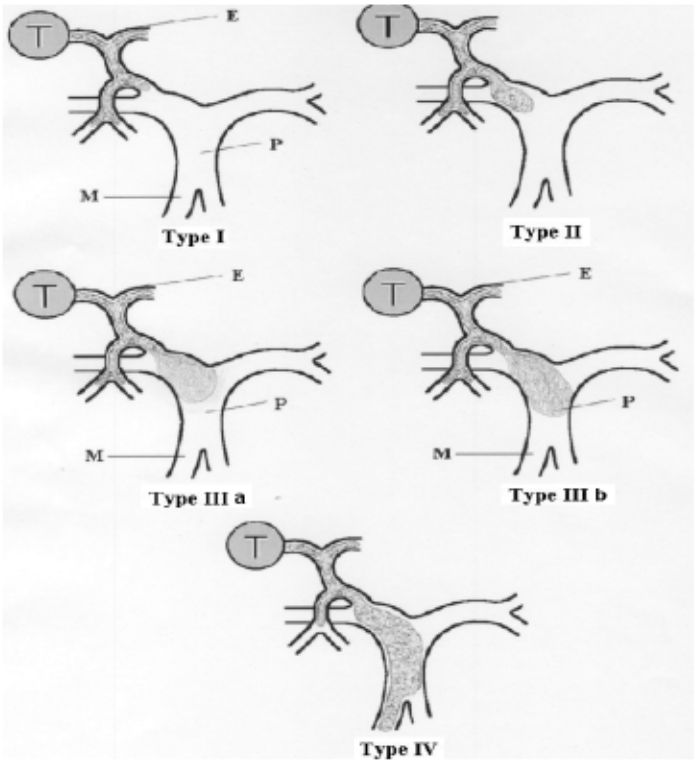


Table 1 Classification of PVT

Types	Subtypes
Type 1o: Tumor thrombi formation found under microscopy	
Type 1: Tumor thrombi involving segmental branches of portal vein or above	Type Ia: Tumor thrombi involving segmental branches of portal vein or above Type Ib: Tumor thrombi involving segmental branches of portal vein extending to sectoral branch
Type II: Tumor thrombi involving right/left portal vein	Type IIa: tumor thrombi involving right/left portal vein Type IIb: Tumor thrombi involving both left and right portal vein
Type III: Tumor thrombi involving the main portal trunk*	Type IIIa: Tumor thrombi involving the main portal vein trunk allowing blood flow to the contralateral lobe (with no thrombosis) Type IIIb: Tumor thrombi involving the main portal vein trunk also occluding blood flow to the contralateral lobe (with no thrombosis)
Type IV: Tumor thrombi involving the superior mesenteric vein	

Note: patients with PVT classifications Type IIIb and Type IV noted above are not eligible under this protocol.

*modified on the basis of extension of the tumor thrombus rather than on the length of the thrombus

3. ECOG Performance Status

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.

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)

5. Brief Summary of Response Criteria Methods

RECIST v1.1 determination of time-point response

Table 1 – Time point response: patients with target (+/– non-target) disease.

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Assessment of Response according to EASL, mRECIST

BEST RESPONSE	EASL *Estimation of reduction in viable tumor volume* *(necrosis= non enhanced area at CT)*	mRECIST *Change in the sum of diameter of viable (enhancement in the arterial phase) target lesions*[4]
CR	Disappearance of all enhanced tumor areas	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	Decrease >50% of enhanced areas	≥30% decrease in the sum of diameters of viable target lesions
SD	Neither CR nor PR nor PD	Neither CR nor PR nor PD
PD	an increase >25% in the size of ≥1 measurable lesion(s)	≥20% increase in the sum of the diameter of viable of target lesion

[4] Does not include summarization of impact of new and non-target lesions on response assessment – see new and non-target lesion response in RECIST v1.1 above for more details

REFERENCES

[1] http://www.cancer.org/downloads/STT/Global_Facts_and_Figures_2007_rev2.pdf accessed June 22, 2010 at 11 :10 ET

[2] European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012 Apr;56(4):908-43.

[3] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129234.htm, accessed June 22, 2010 at 09:30 ET

[4] http://www.nexavar.com/scripts/pages/en/home/pdf/NexavarSmPCEUMar2013.pdf

[5] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Arm. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008 Jul 24;359(4):378-90. PubMed PMID: 18650514.

[6] Chen AL, et al Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advance hepatocellular carcinoma: a phase III randomized, double blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34

[7] Cheng AL et al Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. EJC 2012 Jan 10 [epub ahead of print] doi:10.1016/j.ejca.2011.12.006

[8] Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ; Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008 May 21;100(10):698-711. Epub 2008 May 13. Review. PubMed PMID: 18477802.

[9] http://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf accessed October 28, 2011 at 09:31 ET

[10] http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34552 accessed June 23, 2010 at 10:01 ET M. Sherman, V. Mazzaferro, D. Amadori, J. Seitz, M. Moscovici, M. Shan, A. Nadel, D. Voliotis, J. M. Llovet, J. Bruix, on behalf of the SHARP investigators study arm Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma and vascular invasion or extrahepatic spread: A subanalysis from the SHARP trial. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 4584)

[11] Salem R, Lewandowski RJ, Roberts C et al. Use of Yttrium-90 Glass Microspheres (TheraSphere) for the Treatment of Unresectable Hepatocellular Carcinoma in Patients with Portal Vein Thrombosis. J Vase Interv Radiol 2004; 15:335-345.

[12] Salem R, Lewandowski RJ, Atassi B, et al. Treatment of Unresectable Hepatocellular Carcinoma with Use of 90Y Microspheres (TheraSphere): Safety, Tumor Response, and Survival. J Vase Interv Radiol 2005; 16:1627-1639

[13] Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010 Jan;138(1):52-64. Epub 2009 Sep 18. PubMed PMID: 19766639.

[14] Vente MA, Wondergem M, van der Tweel I et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. Eur Radiol. 2008 Nov 7

[15] Geschwind JF, Salem R, Carr B et al. Yttrium-90 Microspheres for the Treatment of Hepatocellular Carcinoma. Gastroenterology 2004; 127: S194-S205.

[16] Mazzaferro et al Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma : A Phase 2 study Hepatology 2013 ; 57 :1826-1837

[17] Shi J, Lai EC, Li N et al. Surgical Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. Ann Surg Onc 2010 [Epub ahead of print

[18] Shah ZK, McKernan MG, Hahn PF, Sahani DV. Enhancing and expansile portal vein thrombosis: value in the diagnosis of hepatocellular carcinoma in patients with multiple hepatic lesions. AJR Am J Roentgenol 2007; 188: 1320-1323

[19] Rossi S et al. Contrast-enhanced ultrasonography and spiral computed tomography in the detection and characterization of portal vein thrombosis complicating hepatocellular carcinoma. Eur Radio 2008; 18:1749-1756.

[20] http://ecog.dfci.harvard.edu/general/perf_stat.html accessed 3/24/2010; Oken, M.M., Creech, R.H., Tormey, D.C. et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

[21] Fischer L, et al. The segments of the hepatic veins – is there a spatial correlation to the Couinaud liver segments? *Eur J Radiol* 53(2):245-255, 2005.

[22] Data on File – Nordion TheraSphere Reference Binder 2010

[23] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026.)

[24] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010 Feb;30(1):52-60. doi: 10.1055/s-0030-1247132. Epub 2010 Feb 19.

[25] Jennison, C. and Turnbull, B. W. (2000), Group Sequential Methods with Applications to Clinical Trials, New York: Chapman & Hall.

[26] Mehta, C. R. and Pocock, S. J. (2011), Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statist. Med., 30: 3267–3284. doi: 10.1002/sim.4102

[27] Burman and Sonesson (2006), Are flexible designs sound? Biometrics., 62: 664-683

[28] Proschan MA, Lan KKG, Wittes JT (2006), Statistical Monitoring of Clinical Trials: A Unified Approach. 1st edn. Springer: USA