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A Phase II Study using LC Bead LUMI Radio-Opaque Embolic Beads to Detect and Characterize the Vascularity of Hepatic Tumors during Treatment with Transarterial Embolization (TAE) Alone or combined with Thermal Ablation

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Device:

Device Name:	LC bead LUMI Radiopaque embolic beads
FDA 510(k) Clearance:	K152157
Manufacturer:	BTG

PRÉCIS

Background:

- Hepatocellular Carcinoma (HCC) is the 3rd most common cause of cancer globally with an increasing incidence worldwide.
- Management of hepatic malignancies from primary Hepatocellular Carcinoma (HCC) or metastatic disease involves a multidisciplinary approach of surgery and chemotherapy and in the case of HCC, transplant, anti-VEGF sorafenib, or local or regional image guided therapies.
- Thermal ablation (RFA or MWA) and transarterial embolization (TAE) are minimally invasive image guided local or regional therapies that have been extensively studied for decades, and more recently and to a lesser extent have been studied together as a combination therapy.
- LC Bead LUMI™, a radiopaque embolic bead product (company code BTG 13-002), is an imageable spherical embolic product that can be visualised by X-ray based imaging (e.g., fluoroscopy and CT).
- The beads are non-resorbable microspheres with calibrated size ranges that occlude arteries for the purpose of blocking the blood flow to a target tissue.
- LC Bead LUMI™ are intended to be used for the embolization of hypervascular tumors and arteriovenous malformations (AVMs).

Objectives:

- To determine the imaging characteristics of radiopaque beads including qualitatively comparing virtual and actual bead perfusion in the treatment of hepatic tumors using bead embolization.

Eligibility:

- Treatment eligibility for TAE requires agreement between the Interventional Radiologist reviewing imaging and feasibility of TAE and the patient's NIH primary treatment team who will evaluate the patient's clinical parameters to undergo anesthesia and the TAE and or ablation procedure.
- At least ≥18 years of age
- Patients with pathologically proven, hepatic-dominant neoplasm.
- The extent of hepatic metastases is <50% of total hepatic volume.
- Past treatment with Y90 must be 6 months from TAE treatment and liver function within NIH institutional limits
- ECOG performance status ≤2
- Patients must have normal organ and marrow function per laboratory parameters
- Patients with minor allergies to iodine will also be excluded.

Design:

- Number of Participants: 30

- Recruitment Time Frame: ~2 years
- Type of Study: Feasibility study
- This is a pilot study to assess the characteristics of radio-opaque bland beads during TAE in the treatment of hepatic malignancies. Patients may also receive thermal ablation treatment in conjunction with TAE if clinically indicated, although comparison of bead treatment with or without thermal ablation is not part of the study's aim.
- To compare virtual and actual perfusion characteristics of the LUMI radiopaque beads with CBCT and/or CT. Patients' scans will be obtained per TAE standard of care schedule. Other imaging evaluation of this therapy may be performed at regular intervals following completion of treatment, and will be governed by standard conventional imaging regimen post treatment.
- The choice of which combination of imaging (CT, Cone beam CT (CBCT), or fluoroscopy) and when to image, will be made by the clinical care team for the patient, based upon multidisciplinary recommendations and NIH Clinical Center customary use and standard of care, and will be purely clinical decisions (not research-related).
- The participants will have a diagnosed hepatic malignancy, and be eligible to undergo transarterial embolization and thermal ablation under general anesthesia. The LC LUMI bead will be used in the transarterial embolization procedure.
- Follow up will continue for 12 months from the time of initial treatment.
- Patients will be evaluated in multidisciplinary GI medical oncology clinic and up to 30 patients will be enrolled to accrue 20 evaluable patients.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To determine the imaging characteristic of radiopaque beads including qualitatively comparing virtual and actual bead perfusion in evaluating tumor vascularity in the treatment of hepatic tumors using bead embolization.

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1.2 BACKGROUND AND RATIONALE

Management of hepatic malignancies from primary Hepatocellular Carcinoma (HCC) or metastatic disease involves a multidisciplinary approach of surgery and chemotherapy and in the case of HCC, transplant, anti-VEGF sorafenib, or local or regional image guided therapies. The less invasive approaches of transarterial embolization (TAE) or ablation with thermal energy (radiofrequency or microwave) are options that can be palliative or curative. Each approach has its potential for complications that are modest in comparison to surgery.

Treatment of hepatic malignancies with TAE or ablation alone often requires multiple courses because tumor margins are not well delineated by current imaging. Defining tumor locations during the course of an ablation or TAE may enhance accuracy and ability to devascularize the tumor and ultimately causing tumor death. BTG and NIH have collaborated to create a radiopaque bead called LC LUMI bead. These are investigational radiopaque, biocompatible, non-resorbable beads manufactured to be visible under multiple modes of imaging (fluoroscopy, CT, and cone beam CT). BTG PLC International and its subsidiary UK company, Biocompatibles developed the LC Lumi bead under a CRADA with the NIH, and LC Lumi bead is manufactured by BTG PLC, an international specialty pharmaceutical company that is developing and commercializing products targeting critical care, cancer neurologic and interventional medicine. The FDA has granted BTG a 510 (k) Clearance for the LC LUMI beads on December 11, 2015 (see Appendix A, Section **12.1**)

Hepatocellular Carcinoma (HCC) is the 3rdth most common cause of cancer globally with an increasing incidence worldwide [1]. In countries that lack systemic screening for cirrhotic patients, 50-70%, are diagnosed with advanced stage, symptomatic HCC [2]. Liver tumors have historically responded poorly to systemic chemotherapies and radiation, while < 30% are candidates for surgery or transplantation due to inadequate functional liver reserve at advanced disease [3]. In recent years, minimally invasive procedures have been shown effective for certain patients who do not qualify for surgical resection. Thermal ablation (RFA or MWA) and embolization (TAE) are minimally invasive image guided local or regional therapies that have been extensively studied for decades, and more recently and to a lesser extent have been studied together as a combination therapy. The use of TAE without chemotherapy (vs. TACE = with chemotherapy). Thermal ablation and TAE (or TACE) have been used separately or together as acceptable treatments for focal malignancies in the liver [4-7]. Local and regional therapies may provide benefits in comparison to traditional cancer treatments, with reduced morbidity and mortality, can be performed on an outpatient basis, repeated over time, and used in conjunction with other cancer treatments [8].

Metastatic cancer to the liver is common from primary liver cancer, neuroendocrine tumors, colorectal, lung, and urogenital cancers (adrenal, kidney, and bladder) and are treated with embolization and or ablation, often with the goal of debulking of palliation.

Thermal ablation and TAE attack different components of the tumor and can work synergistically to create an additive effect of treatment, potentially resulting in a more robust response.

Thermal ablation treats the center or "inside" of the tumor, potentially leaving behind a viable hypervascular margin sub-lethally treated secondary to the "heat sink effect" [9-11]. This hypervascular margin on the "outside" of the tumor is the target of embolization which targets and embolizes the vasculature, potentially eliminating this viable margin [12, 13].

RFA and MWA produce tissue death through hyperthermic injury. Coagulation necrosis occurs from an alternating high frequency electric current in the radiofrequency range (460-500 kHz). This is delivered via an electrode placed directly in the target lesion and the movement of ions within the tissue creates frictional heat as the ions try to follow the alternating current [14]. RFA is currently the most common ablative therapy, recommended for lesions ≤3cm (single or up to 3 lesions) and single lesions ≤5cm who are not candidates for liver resection or liver transplant, but have preserved liver function [7]. This results in very narrow indications. The major limiting biological factor to thermal ablation is hepatic blood flow. The body temperature blood in adjacent tumor blood vessels is relatively cooler than the ablation zone, leading to conduction of thermal energy away from the target tissue and into the blood. The result is limited heating of perivascular tissue and subsequent irregularly shaped treatment spheres of ablation [10, 15]. This "heat sink" effect results in sparing of tumor cells nearest the blood vessels, with subsequent tumor regrowth. Given this phenomenon, different methods of hepatic blood flow reduction, and direct treatment of perivascular cells with regional chemotherapy have been developed, including TACE or DEBs.

MWA uses electromagnetic energy creating a rapid and homogeneous heating of tissue and subsequently coagulation necrosis. Another mechanism of MWA function is ionic polarization with conversion of kinetic energy into heat. A more homogeneous, larger ablation zone that is easily predicted is feasible and the heat- sink effect is attenuated. One reason for the reduced heat-sink effect may be the faster heating and higher temperatures provided by microwave energy. Notably, the ablation heat beyond the microwave field is conducted in a similar way as in RFA with the heat- sink effect still present. Another consequence of the different production of heat seen with MWA is that the time needed for ablation is less in MWA than that required in RFA.

Transcatheter arterial embolization is a standard treatment option for patients with unresectable primary hepatocellular carcinoma (HCC) and is used to treat some liver metastases. Despite the widespread use and success of embolization for more than three decades, there remains a lack of consensus regarding optimal technique. For example, there is variability in (i) type and size of embolic agent, (ii) use of chemotherapeutic agent(s), (iii) degree of catheter selectivity, and (iv) optimal embolization endpoint. This material and technical variability may be perpetuated by a lack of knowledge concerning the influence of these embolization variables on patient outcomes. Educated recommendations to standardize material choice and procedural technique may be formulated if embolic material and drug locations inside the embolized tissue were known with a high degree of confidence.

Although extensive experience has been accumulated for both RFA and TACE or DEBs for the treatment of a variety of liver tumors, the reoccurrence rates of liver lesions treated with each alone have been reported to be quite high, largely depending upon patient selection and size and

number of lesions. Since each treatment attacks the tumor in different ways, it could potentially be more effective than either alone.

Studies in the literature have already implemented combination therapy of RFA and TACE or DEBs and shown it to be both feasible and safe [1, 16-19]. These studies have thus far shown improved progression free survival with tumors ≥ 3cm with combination therapy as compared to RFA alone. They have also shown that overall survival is improved with tumors > 5cm, and that combination therapy is comparable to RFA alone along all tumor sizes [16, 18, 20]. Although these studies have shown combination therapy to be safe and feasible, there is currently no standard convention for how to most effectively combine the two. Studies have completed TACE followed by RFA same day, 1 week or up to 3 to 4 weeks after the initial procedure. Other studies have performed RFA followed by TACE. Coming to a conclusion of overall effectiveness from these varying protocols is challenging and more studies are needed to assess a standard convention.

Additionally, subject treated with Y90 at least 6 months prior to treatment and meet all other eligibility requirements will be eligible. These subjects were ineligible initially due to concerns of Y90 induced hepatic dysfunction and uncertainty of LUMI LC beads additive effects.

1.2.1 Virtual Perfusion

Another factor during treatment of HCC and liver metastases with TAE is the ability to accurately determine the vessels for embolization and to effectively perfuse the selected vessels with beads during the procedure. Limited tumor vascularity and overlapping vessels can pose a challenge in determining the ideal location necessary for embolization with beads. EmboGuide a FDA-approved software medical device, will be used to assist the physician performing the procedure by having the functionality to analyze tumor vascularity, and the capability to identify and annotate the feeding vessels intended for embolization. The software will enable comparison for the actual and virtual perfusion characteristics of LUMI beads during embolization.

1.2.2 LC Bead LUMI™

LC Bead LUMI™, a radiopaque embolic bead product (company code BTG 13-002), is an imageable spherical embolic product that can be visualized by X-ray based imaging (e.g., fluoroscopy, CBCT, and CT). The beads are non-resorbable microspheres with calibrated size ranges that occlude arteries for the purpose of blocking the blood flow to a target tissue. LC Bead LUMI™ are intended to be used for the embolization of hypervascular tumors and arteriovenous malformations (AVMs).

1.2.3 Summary and Rationale

LC Bead ™ microspheres are indicated for embolization of hypervascular tumors and have been commonly used for embolization of liver tumors. Certain hepatic-dominant hypervascular neoplasms may be treated with minimally invasive image guided therapies ablation and transarterial embolization. In the past, LC beads were not made visible on x-rays, therefore the physician was unable to visualize the exact location of the beads. Lumi beads are basically LC beads with iodine, so they can be visualized on x-ray or CT, and show the physician where the beads are going. Characterizing the bead appearance on x-ray, fluoroscopy, and CT could inform future treatments by identification of tumor at risk for under-treatment, which may also help targeting for further treatment (sometimes with RFA), or for follow up.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

Patients will be screened for this study only after the patient has been determined eligible for the TAE procedure by the referring/ primary team and an interventional radiologist.

2.1.1 Inclusion Criteria

2.1.1.1 Patients who are determined to be eligible for TAE by an interventional radiologist and the primary/referring team will be eligible for the study.

2.1.1.2 Patients with pathologically proven hepatic-dominant neoplasm that might otherwise be candidates for standard clinical TAE.

2.1.1.3 Extent of hepatic metastases is <50% of total hepatic volume.

2.1.1.4 At least ≥18 years of age: Because it is exceeding rare for someone under the age of 18 to develop hepatocellular carcinoma, we will exclude patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

2.1.1.5 ECOG performance status 0-2

Six months since last treatment with Y90

2.1.1.6 Patients must have normal or adequate organ and marrow function as defined below:

	Laboratory tests	Inclusion Criteria
Hematology	Absolute Neutrophil Count	> 1500 / mm^3 without help of Filgrastim or other stimulating growth factors
	Platelet Count	Patient eligible if platelet count is correctable to ≥50,000/mm3
	Hemoglobin	Patient eligible if hemoglobin count is correctable to ≥ 8.0 g/dl
Serum Chemistry	ALT/AST	≤ 5 times the upper limit of normal; except in the presence of obstructive liver metastases where ALT/AST may be up to 10 times the upper limit of normal
	Creatinine	<1.5x institution upper limit of normal OR creatinine clearance ≥ 45mL/min/1.73 m2 for patients with creatinine levels above institutional normal.
	Total Bilirubin	≤ 3 mg/dl
	Prothrombin Time	within 2 seconds of the upper limit of normal (INR≤1.8)

2.1.1.7 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.8 Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause.

2.1.2 Exclusion Criteria

2.1.2.1 No contraindications to receive iodine products.

2.1.2.2 Main Portal Vein Occlusion or other contraindications to chemoembolization

2.1.2.3 Prior selective internal radiation therapy (SIRT) with 90-Y of more than one treatment per lobe or a single whole liver treatment less than 6 months from proposed treatment.

2.1.2.4 Patients taking immunosuppressive drugs or unable to come off of ongoing chronic anticoagulation will not be eligible.

2.1.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection with systemic manifestations, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.6 Pregnant women and nursing mothers are excluded from this study because of the potential for teratogenic or abortifacient effects of required multiple imaging and associated radiation doses, anesthesia and risks during thermal ablation to the fetus. Enrolled patients must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

2.1.3 Recruitment Strategies

Potential study candidates may be referred from other NIH clinical studies to treat liver cancer. This study is "Enrolling by invitation only".

2.2 SCREENING EVALUATION

Patients will be screened and evaluated for ability to undergo the TAE procedure by the referring physician or primary team prior to referral to this study. All screening procedures to determine if a patient is eligible for the TAE procedure, including but not limited to imaging scans, labwork, and pre-anesthesia evaluation, will be performed , ordered, reviewed and documented in the electronic medical record (CRIS) by the referring/primary team per routine clinical care. After completion of screening evaluation procedures, the primary or referring team and an interventional radiologist or his designee will document that the patient is eligible for TAE (and thermal ablation, if applicable) and direct enrollment onto this study.

2.2.1 Research Team Screening Responsibilities

Prior to enrollment in this study, the research team will review the following and place a note in CRIS of patient's eligibility:

1) H&P
2) Imaging – may include CT of the abdomen and pelvis, MRI of the abdomen, MRI/PET or CT/PET, and US of the abdomen.
3) Laboratory results

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Commented [GC([2]: Can we delete this? We will need a justification for removal.

2.4 TREATMENT ASSIGNMENT AND RANDOMIZATION/STRATIFICATION PROCEDURES

Cohorts

Number	Name	Description
1	*Patients*	*Patients who have primary or metastatic liver cancer*

Arms

Number	Name	Description
1	*Experimental*	*Treatment of hepatic tumors using bead embolization*

Randomization and Arm Assignment

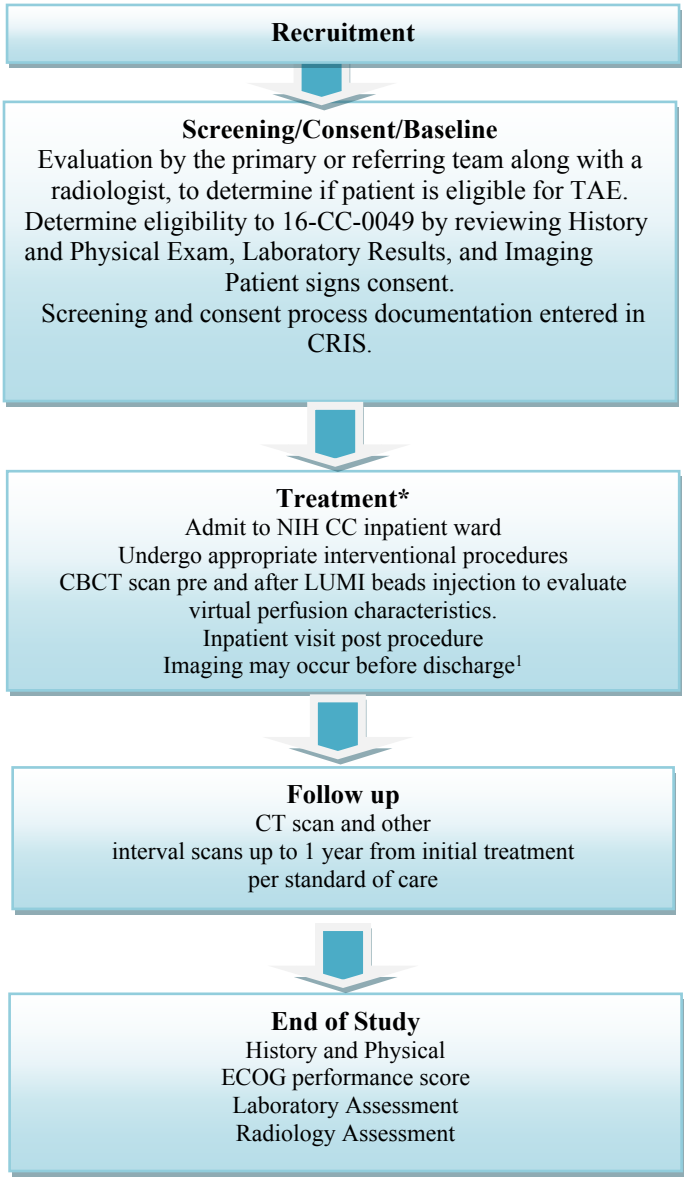
Patients in cohort 1 will be directly assigned to arm 1

2.5 PRE-OPERATIVE (BASELINE) EVALUATION

- Review of history and physical exam
- Review of laboratory results

3 IMAGING STUDIES STUDY IMPLEMENTATION

3.1 STUDY DESIGN



[1]as clinically indicated
*Patients may require re-treatment

3.2 PROCEDURE

Patients will be admitted to the NIH inpatient oncology ward and then brought to the interventional radiology suite where consent for both procedures and anesthesia using standard NIH consents will be obtained.

Standard transarterial embolization using LC Bead LUMI (Biocompatibles UK Ltd) Radiopaque Embolic radiopaque, biocompatible, non-resorbable, hydrogel beads typically with thermal ablation (microwave or radiofrequency) in an order appropriate to the clinical picture, will be administered in the Interventional Radiology Section under general anesthesia provided by the Clinical Center Department of Perioperative Medicine (DPM). Patients will remain primarily under the care of their primary team, typically NCI medical oncology service, or surgical oncology service.

The use of thermal ablation devices (RFA or MWA) and transarterial embolization will be according to manufacturer's instructions and the standard of care at the institution. Thermal ablation treatments will be administered according to the thermal ablation device instructions and the Standard of Care of the IR/CC/ NIH. The choice of which device to use will be at the discretion of the physician performing the procedure based on the factors particular to the patient's lesion(s). TAE will be administered with LC LUMI beads in accordance with the TAE device instructions and the Standard of Care of the IR/CC/ NIH and will be administered after an ablation treatment. Retreatment may be done at the recommendation of the physician, according to conventional standards. Multiple lesions may be treated with TAE with LC LUMI beads with or without thermal ablation.

3.2.1 Ablation and Embolization Procedure

During this clinical protocol, standard thermal ablation performed with general anesthesia, and CT and ultrasound guidance, often to include fusion guidance ("Medical GPS"). At the NIH, thermal ablation will be conducted according to the standard of care and practice guidelines that have been in effect for TAE and RFA treatment procedures at the CC since 1998.

TAE is the most common procedure used to treat HCC. The process involves cannulating tumor nourishing vessels and occluding the blood supply using materials such as beads, that can be combined with anti-neoplastic agents or not. The procedure involves arteriography of the superior mesenteric and celiac vasculature to identify a roadmap of vessels and vascular anomalies (accessory or replaced hepatic vasculature), confirm portal vein patency, and identify hepatic arterial anatomy. This is typically followed by a selective common hepatic arteriography to recognize non-target vessels supplying the pancreas, duodenum, or stomach. Relevant non-target vessels that cannot be excluded by distal catheter tip positioning may be selectively embolized to prevent unintended chemoembolization. For patients with multifocal disease or tumors that span both lobes, embolization of each lobe may be performed in two or more separate treatment sessions. The selected hepatic lobar artery (typically right or left) will be

catheterized for TAE with LC LUMI beads. An attempt will be made to exclude the cystic artery from the embolization distribution. Extrahepatic branch vessels may be prophylactically embolized at the discretion of the Principal Investigator to mitigate the risk of non-target deposition of LC LUMI beads. TAE will continue typically until near-complete flow stasis is observed in the target artery (where no non-target reflux of contrast material into more proximal branches is observed). If significant antegrade flow is observed in the target artery following procedure, additional embolization using LC LUMI beads may typically be added to reach the embolization endpoint. Visibility of the LC LUMI beads will be recorded using a 3 point scale: 0, definitely not visible; 1, probably visible; and 2, definitely visible. A CBCT scan *may* be obtained post LUMI beads injection to evaluate virtual perfusion characteristics of the beads for predictive investigations of their delivery and function.. The catheter will then typically be retracted into the common hepatic artery and completion arteriography will document the degree of target vessel flow stasis and non-target vessel patency.

Thermal ablation therapy may be administered based on the clinical evaluation of the patient and when appropriate will be done according to the manufacturer's instructions for use. After infiltration of the skin (for percutaneous approach) with a local anesthetic, the needle of the chosen system will be directed into the lesion, with image guidance and the needle is confirmed to be in the lesion by imaging. After confirming appropriate positioning, the lesion will be heated typically for 10-15 minutes, according to manufacturer's guidelines. The exposure time may be varied depending on the temperatures achieved and proximity of adjacent anatomy or other patient-specific anatomy or issues. Depending on the size of the lesion to be ablated, multiple locations of the needle as well as multiple ablation cycles will be performed in order to ideally achieve an approximately 1-cm margin of ablated tissue around the lesion or target volume. Adequacy of ablation will be followed by ultrasound throughout the procedure, when possible. Depending on the size of the lesions and the time required to complete the ablation, multiple lesions may be treated, often as staged procedures.

3.2.2 Post Ablation and Transarterial Embolization Care

During hospitalization, the patients will be admitted to the patient care unit following interventional procedures for routine post-procedure monitoring and inpatient care. Antibiotics, anti-emetics, hydration and comfort medicines will be administered based on the patient's clinical status. Laboratory study including a CBC, hepatic panel (alkaline phosphatase, bilirubin, AST and ALT), acute care (Na, K, CL, CO2, BUN, Cr), and Mineral panel (Mg, albumin, Phos, Ca,) will be typically obtained upon admission and daily post procedure, while in the hospital, according to standard clinical practice. Immediate imaging may occur if clinically indicated, based on the patient's clinical status and at the PI's discretion, as is standard of practice. Length of stay will be based on clinical status of the participant and the discretion of the PI

3.2.3 Follow up Procedures

Subsequent Clinical Center visits following treatment for study participants will be determined in accordance with the participants' primary medical or surgical oncology team and in collaboration with the study PI, as clinically indicated.

Imaging and laboratory assessments will be typically repeated as clinically warranted during the12 months after initial treatment, or at least until evidence of disease remission, stabilization or recurrence or residual disease is documented. A CT scan will be obtained within 2 months post treatment to evaluate virtual perfusion characteristics of the LUMI beads.

3.2.4 Study Stopping Rules

Enrollment will be halted and the IRB notified if:

- Three or more patients with a non-laboratory grade 4 toxicity within the first 72 hours post TAE whether or not considered TAE or research-related.
- Death due to any cause within the first 72 hours post TAE.

All patients will be monitored until there is improvement or resolution of toxicity. Once the IRB, has completed their review; they must give their permission for the study to resume.

3.3 TYPICAL STUDY CALENDAR*

Procedure	Screening	Pre-operative evaluation prior to receiving LUMI beads treatment	Treatment	Post Treatment	Follow up
			Day 0 to discharge or until off treatment[b]	Within 2 months post treatment	Any time point up to 12 months from initial treatment
Procedures performed by the Referring/ Primary Team					
Evaluation to determine if patient is eligible for TAE	X				
H&P to include baseline symptoms, concomitant medications, etc.	X				
Labs	X				
Procedures performed by the Research Study Team					
Consent	X				
Review of Radiological Assessments [a]	X	X	X	X	X
Review of H&P, labs, and concomitant meds		X			
TAE (if appropriate may include thermal ablation)			X	X[c]	X[c]
Response Evaluation			X	X	X
Adverse Events			X	X[d]	X[d]

[a] CT/ CBCT, MRI, or PET scan. All radiological imaging to be performed as clinically indicated and based on the status of the patient.
[b] Off treatment is 72 hours post TAE.
[c] Patient may require repeat procedures
[d] See section 4.1.4 for AE data collection and management during the follow up period.
* Primary teams determine course of follow up, but usually request treating Interventional Radiologist input.

3.4 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.4.1 Criteria for removal from protocol therapy

- Toxicity that prevents further imaging (e.g., renal dysfunction as serum creatinine >2.0mg/dl and precludes CT or MRI imaging)
- Patients will be considered "off treatment" 72 hours following TAE
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in section **3.2.4**
- Investigator discretion

3.4.2 Off-Study Criteria

- Inability to complete a single session of TAE
- Completed 12-month follow-up period
- Participant requests to be withdrawn from study
- Loss of capacity to provide informed consent
- Death
- Patient becomes eligible for hepatic surgical resection, transplant, or other treatment.

Eligible candidates who have signed the consent and become unable to undergo treatment (due to rapid progression of diseases, etc.) will come off the study. CRO will be notified of the off study reason.

3.4.3 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 DATA COLLECTION AND EVALUATION

4.1 DATA COLLECTION

All data will be kept secure. The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability Act, eligibility and consent verification will be recorded. Primary data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed for 30 days or until return to baseline or stabilization of event.

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS and FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

4.1.1 Baseline Data Collection

Following consent, participating patients will typically undergo a CT of the chest abdomen, and pelvis, as clinically warranted. Additional imaging may be obtained if clinically indicated by the treating interventional radiologist, to identify the target area. Previous imaging may also be used as baseline scans if they fall within the allowed protocol timeframe. Standard baseline information which typically includes demographics, disease history, and previous therapy for liver malignancies will be collected.

4.1.2 On Study Data Collection

We will also document bead visibility data during embolization. This information will be collected using a qualitative particle visibility scale by applying a 3-point scale: 0, definitely not visible; 1, probably visible; and 2, definitely visible [21].

Intra-procedural, post treatment, and follow up images will all be saved and stored in PACS. Patient images will be anonymized prior to transfer to a secure work station for analysis. CRF's and non-image data will be stored in the DRD shared drive which has limited access. The DRD shared drive is backed up and managed by the NIH DCRI in keeping with the protection and confidentiality guideline of the Privacy Act of 1974.

Any grade 3 events and higher occurring up to 72 hours post treatment (either with combined RFA and TAE or with TAE alone) will be collected and recorded in the study database as adverse events, except those listed in the Exclusions to Adverse Event Data Collection section (see Section **4.1.3**). Grade 2 events will be collected and recorded if not resolved before the patient is considered off treatment (72 hours post treatment). Grade 1 events will not be collected or reported.

4.1.3 Exclusions to Adverse Event Data Collection

The following adverse events are expected events from the procedure and study device and will not be collected unless the nature, severity, and frequency are deemed by the PI as unexpected for this patient population.

Anticipated adverse events related to TAE:

- Fever
- Right upper quadrant pain
- Acute cholecystitis
- Acute pancreatitis or elevation of amylase and lipase
- Nausea
- Vomiting
- Fatigue
- Elevated white blood cell count
- Elevated liver enzymes
- Bleeding
- Groin hematoma
- Arterial dissection
- Portal vein thrombosis
- Pleural effusions
- Aspiration pneumonia from intubation
-

Anticipated adverse events related to ablation procedure:*

- Pain at the site of ablation needle insertion
- Muscle ache
- Fever
- Fatigue
- Nausea
- Vomiting
- Elevated liver function tests
- Hyponatremia following hydro-dissection
- Thrombocytopenia and anemia post-RFA
- Pleural effusions
- Aspiration pneumonia from intubation
- Bleeding

*If ablation is given

Anticipated adverse events related to LC LUMI beads (will collect if grade 3 or above):

- Allergic reaction to LC LUMI beads

4.1.4 Follow up of Adverse Events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and / or referral to the general physician or medical specialist.

The investigator will evaluate reported adverse events for determination of seriousness and causal relationship with the treatment or the device.

4.1.5 Device Records

Records or receipt, use, and disposition of the LC Lumi Radiopaque Embolic beads will be kept according to 21CFR 812.140 (a).

- The size, batch number, and expiration date will be recorded for each patient.
- The name of the person who received and used the beads will be documented. Disposal of beads, if unused, will also be recorded as well as the person's name who handled the disposal.
- Any bead deficiency will also be recorded along with the correspondence with the manufacturer.

4.1.6 Handling and storage of data and documents

All individual patient data and records will be collected and maintained on confidential basis and according to the applicable national data protection, privacy, and security laws. Data collected from subjects enrolled in this protocol may be used in submissions to regulatory agencies, and for publications. Summaries of data and information from each patient data form may be used for statistical analysis of the investigation's finding during trial.

Trial data will be recorded in a database during the trial. Each patient will receive a unique study ID. The study investigator shall safeguard a list linking subject names to their ID numbers. Access to the database is restricted to personnel involved in conducting the trial. Final trial data for the report is expected to be in the database within 3 months from completing the last patient's follow-up.

The study investigator will also be responsible for maintaining all correspondence pertaining to the investigation. All shipment, receipt, and disposition of the study device will be kept in the electronic regulatory binder. Also kept in the regulatory binder are signed investigator agreements, study investigators' OSHRP training certificates, and COI records.

4.1.7 Record Retention

The investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational device.

4.2 DATA SHARING PLANS

4.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_X_ De-identified data in BTRIS (automatic for activities in the Clinical Center)

_X_ De-identified or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

X An NIH-funded or approved public repository. Insert name or names: clinicaltrials.gov.

X BTRIS (automatic for activities in the Clinical Center)

X Approved outside collaborators under appropriate individual agreements.

X Publication and/or public presentations.

When will the data be shared?

X Before publication.

X At the time of publication or shortly thereafter.

4.3 RESPONSE CRITERIA

4.3.1 Definitions

- Evaluable for bead visibility: All patient imaging will be evaluated for the visibility of the LC LUMI beads using a 3 point scale: 0, definitely not visible; 1, probably visible; and 2, definitely visible as defined the treating interventional radiologists. Other characteristics may be noted such as the radiopacity of the beads, visibility of the beads in the tumor, overall location of beads in relation to the tumor or targeted site.
- Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their treatment with LC LUMI radiopaque beads up to 72 hours post completion of treatment. Grade 3 or greater adverse events, including allergic reactions, collected during this time period, will be followed until resolution. Expected or anticipated adverse events from the research or the study device will not be collected. See Section **4.1.3** for details.
- Evaluable for imaging characteristics: Only those patients who are eligible for the study, have received at least one treatment of TAE, and have had their disease re-evaluated per standard of care imaging will be considered evaluable.

4.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

5 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

5.1 DEFINITIONS

Adverse events and serious adverse events are defined for this study following the standard ISO 14155:2011 for Good Clinical Practice in clinical investigation of medical devices for human subjects.

5.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

5.1.2 Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of the LC Lumi Radiopaque embolic beads.

Serious Adverse Event (SAE) is an AE that results in the following:

- death
- serious deterioration of the subject's health, leading to
    - life-threatening illness or injury, or
    - permanent impairment of a body structure or function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment of a body structure or function
- fetal distress, fetal death or a congenital abnormality or birth defect

5.1.3 Serious Adverse Device Effect (SADE)

A serious adverse device effect (SADE) is an ADE that results in any of the consequences characteristic of an SAE. An unanticipated SADE (USADE) is a SADE which is not anticipated by the risk analysis, while an anticipated SADE (ASADE) is a SADE which is anticipated by the risk analysis.

5.1.4 Unanticipated adverse device effect

Defined as any **serious adverse effect** on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), other unanticipated serious problem associated with a device that relates to the rights, safety and welfare of subjects.

5.1.5 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

5.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

5.1.7 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

5.1.8 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

5.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

5.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

5.2.1 NCI-IRB and Clinical Center CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB and CC Clinical Director:

- All deaths, except deaths due to progressive disease
- All Serious Protocol Deviations
- All Unanticipated Problems
- All serious non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

5.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

   NOTE: Grade 1 events are not required to be reported.

5.3 EXPEDITED ADVERSE EVENT REPORTING CRITERIA TO THE MANUFACTURER

The manufacturer will be responsible for all safety reporting related to the use of LC LUMI beads.

The Investigator shall, in accordance with all Applicable Laws and regulations, report all and any unanticipated serious adverse events and/or device malfunctions that are at least possibly related to the investigational device and/or the investigation to Company within twenty four (24) hours

of such adverse events and/or device malfunctions occurring, and to the relevant authority or authorities as shall be required by all such Applicable Laws and regulations (guidance to which may be provided in the Protocol). Investigator shall also provide Company with any other information and assistance as may be requested and/or required by Company to allow Company to comply with its reporting obligations.

All adverse event data will be forwarded to pharmacovigilance@btgplc.com

5.3.1 Investigator Responsibilities

The Investigator will conduct the study in accordance of the investigational plan, any IRB-imposed conditions, and applicable FDA regulations for protecting the rights, safety and welfare of subjects under the investigator's care, and for obtaining informed consent from each research participant prior to any study related procedures. Investigators are also responsible for maintaining control of the investigational device. The Investigator will also assure monitoring is conducted according to the monitoring plan. IRB approval of the study must be obtained prior to study start and this documentation will be on file. The Investigator will promptly notify the IRB of any significant new information about this investigation.

This clinical study is being conducted at Clinical Center National Institutes of Health. Investigators may determine if potential subjects would be interested in taking part in the investigation but written informed consent will not be obtained from study participants and study participation will not be allowed prior to IRB approval.

The investigational device will only be used on research subjects with the investigator's supervision and will not be used on any person who is not authorized under 21CFR812 to receive it.

5.4 DATA AND SAFETY MONITORING PLAN

5.4.1 Principal Investigator/Research Team

The clinical research team will meet on a routine basis when patients are being actively treated on the trial to discuss each patient. Decisions about ongoing enrollment and intervention will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations/reportable events will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

5.4.2 Monitoring Plan

Accrual and safety data will be monitored by the principal investigator, who will provide oversight to the conduct of this study. The PI will continuously evaluate implementation of the protocol for any unusual or unpredicted complications that occur and will review the data for accuracy and completeness.

6.0 QUALITY ASSURANCE

The NIH Clinical Center's quality assurance program will conduct study monitoring at least annually or more frequently as required. Patient consent documents, primary outcome and safety laboratory results and diagnostic test results will be monitored for accuracy, correct dating, and agreement between case report forms and source documents. All regulatory reports, reviews and amendments, adverse events, problem reports related to study, the investigator credentials, training records, and the delegation of responsibility log will be reviewed during monitoring visits. Any major findings will be summarized in writing and reported to the study pi who will be responsible for submitting the monitoring report to the IRB.

7.0 STATISTICAL CONSIDERATIONS

This is a proof of concept/feasibility study with a small number of evaluable patients and data points. Data collected will not be sufficient to provide meaningful statistical analysis.

Sample size was derived from historical experience with pilot feasibility observational studies, where a population of 20-30 evaluable patients should provide initial information to begin to characterize the imaging features of the approach, which is the main goal. This should allow for adequate slight variations in dosages and anatomy to inform such a pilot study. The precise characterization of the imaging features will require a much larger future study, but this pilot study outcomes and imaging features could be used to power future studies, depending upon the primary aims. No statistical analysis is required to power this trial, as it is a pilot feasibility study, and the outcomes related to imaging features will not be statistically analyzed, other than simple descriptive statistics. Descriptive statistics will be provided in summary tables.

- Categorical variables will be summarised using frequency distribution: number of observations (N) and percentages (%).
- Continuous variables will be summarized using standard quantitative statistics:
    - number of observations (N),
    - mean, standard deviation (STD),
    - median and
    - range (minimum and maximum observed values).

When relevant, the 95% confidence intervals (CI) will also be displayed.

For instance, qualitative analyses may be done to compare virtual and actual perfusion characteristics (such as overlap) of LUMI beads using CBCT before, during, and after LUMI beads injection.

If fewer than 20 evaluable patients are enrolled, then the variety of imaging features seen may be limited. Using fewer than 20 evaluable patients could start to substantially compromise the ability of the study to provide the necessary rationale for further work in refining and developing the clinical use of this approach. Since the emphasis is that this is a PILOT study, this recommended study size of N=20 EVALUABLE patients seem to be a good compromise. Lastly, assuming that possibly up to 33% of recruited patients may turn out to either be ineligible or that their data will be inevaluable, a total of N=30 patients will need to be recruited to ensure having (roughly) 20 evaluable patients. If a patient's follow-up imaging is not available but their procedural data is adequate they will be considered evaluable. Inevaluable patients are defined

as patients whose data cannot be reliably recorded in terms that satisfy the primary endpoint. This could occur if the data cannot be graded in terms of visibility due to technical issues such as patient motion or small doses of beads used in a small volume of tissue.

8 COLLABORATIVE AGREEMENTS

8.1 CRADA

The investigational study device is provided by another party under a Collaborative Agreement [Cooperative Research and Development Agreement (CRADA) with BTG/Biocompatibles UK Limited (#08-02412).

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

This study intends to enroll 30 participants who have primary or metastatic liver cancer. The study seeks to enroll both women and men who meet eligibility criteria including whites, non-whites and minorities. Patients who may be unable to comprehend the study requirements and associated risks may not be able to be enrolled. The intent of this study is a proof of concept safety and feasibility study and as such, children would not be the appropriate patient population.

9.1.1 Selection Based On Gender, Ethnic, Race

Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. Efforts will be made to extend accrual to a representative population. Statistical analysis to explore ethnic, race and gender differences will not be performed, as this study is not powered to explore any such differences.

9.1.2 Justification for Exclusion

Patients that are pregnant will be excluded from this trial because of concern that ionizing radiation may be harmful to the developing fetus. Patients with altered mental status that prevents consent or answering questions will be excluded. Patients with uncorrectable coagulopathies may be at increased risk for bleeding, and will be excluded. Patients with multiple co-morbidities, sepsis, or multiple high-risk medical problems may be at increased risk for morbidities or mortalities, and will be excluded. This does not change standard transarterial embolization exclusions.

9.2 PROTECTION OF PATIENT RIGHTS

The Radiology and Imaging Sciences Department is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the patient's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the Informed Consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits. The IRB must give full board approval of the protocol and consent documents before the study may begin at a site.

9.2.1 Confidentiality

The Radiology and Imaging Sciences Department is responsible for the confidentiality of the data associated with patients registered/randomized in this study in the same manner it is

responsible for the confidentiality of any patient data within its sphere of responsibility. For patients registered/randomized to this study, there are additional considerations related to the necessity of sharing of research data with the ACOSOG-CC and representatives of NCI and OHRP.

9.3 PARTICIPATION OF CHILDREN
Children will not be eligible for this study.

9.4 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT
Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. In these cases, the subject will be taken off study.

9.5 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS AND RISKS/BENEFITS ANALYSIS
The risks inherent to this device itself should be identical to the risks of undergoing the clinically indicated procedure, and are outlined in detail below. This use of beads for embolization has been standard therapy for liver tumors for decades. The LUMI bead is very similar in composition to the widely used over the last decade and commercially available LC bead™. The LUMI LC bead is basically an LC bead with attached iodine to make it visible on x-rays, like regular iodine contrast. The risks of these LUMI LC beads are discussed in the table below:

No	***Potential Hazard***	***Resultant Harm***	***Risk Evaluation Discussion***	***Mitigation Strategy***
1	*Transarterial embolization Thermal ablation*	• *Pain* • *Bleeding* • *Infection* • *Nausea* • *Anesthesia complications* • *Pneumothorax* • *Liver abscess formation* • *Acute cholecystitis* • *Gastric ulceration* • *Pancreatitis* • *Misembolization* • *Radiation Injury* • *Allergic reactions to anesthesia medications* • *Allergic reaction to intravenous contrast* • *Liver failure* • *Stomach ulcer* • *Postembolization syndrome (24-72 hours following chemoembolization , during hospital*	*The LC beads will be placed using standard of care transarterial embolization protocol. The tumor site is accessed via an inguinal artery*	*Pre-operative clearance from the anesthesia service.* *Pain and Palliative care consult as clinically indicated* *Evaluation of any outstanding cardiology, pulmonology or other co-morbid disease states before IR procedures; routine general sedation and peri-operative, antiemetics, antacids, antibiotics, local anesthesia and post operative patient controlled analgesia, bedrest, nursing surveillance and antibiotics.* *Patients with known contrast allergies will be pretreated per standard of care* *Patient with known allergies to any anesthesia agents will receive comparable anesthesia medications that they can tolerate* *Peri-procedure imaging to evaluate immediate LC bead placement enhanced by the beads radiopaque element will allow immediate visualization*

No	***Potential Hazard***	***Resultant Harm***	***Risk Evaluation Discussion***	***Mitigation Strategy***
		observation period) • *Abdominal visceral injury (from non-target embolization, 1-2 weeks following embolization):*		*of misembolization. Patient are admitted to the inpatient hospital ward during the immediate post-operative period and monitored. Post-operative changes in patient comfort vital signs or diagnostics such as liver enzymes will prompt further evaluation.*
2	*LC Lumi beads*	*Allergic Response*	*The preclinical experience does not raise concerns that the radiopaque LC beads produces any known acute allergic response (see Investigator's Brochure).*	*Patient with known allergy to LC beads or its components will be excluded from the study*
3	*LC Lumi beads*	*Endotoxin adverse reaction*	*The preclinical experience does not raise concerns that the radiopaque LC beads produces any known acute endotoxin response (see Investigator's Brochure).*	*Labeled non-pyogenic Endotoxin testing in animal models proved no change in temperature during an observation period following injection of extracted LC bead LUMI. Acutely febrile patients will be excluded from the procedure as is standard of care*
4	*LC Bead LUMITM Bead*	*Genotoxicity, Carcinogenicity, reproductive toxicity*	*The preclinical experience does not raise concerns that the radiopaque LC beads produces any known genotoxicity, carcinogenotoxic or reproductive toxic adverse events (see Appendix C, Section **0**)*	*Patients who are of reproductive age will be counseled on use of adequate birth control. All women who are of reproductive age and are not sterile or post-menopausal will be tested for pregnancy prior to all imaging.*
5	*LC Bead LUMITM beads*	*Systemic or local toxicity*	*The preclinical experience does not raise concerns that the radiopaque LC beads produces any known acute systemic or local adverse response (see Appendix C, Section **0**)*	*Patient are admitted to the inpatient hospital ward during the immediate post-operative period and monitored. Post-operative changes in patient comfort, physical exam, vital signs or diagnostics such as liver enzymes will prompt further evaluation with imaging and immediate treatment.*

9.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

All patients who are being considered for this trial will undergo informed consent prior to being enrolled in the trial, as well as evaluation by multi-disciplinary review.

During the initial consultation, the patient, along with family members, is presented a forthright and detailed overview of the treatment options available to them at the NIH. The experimental nature of the treatment, its theoretical advantages and disadvantages, and an overview of the procedure and anticipated convalescence are presented. The Informed Consent document is given to the patient and they are asked to review it, make notes and follow-up with a phone call to the physician or nurse investigator to have any additional questions answered prior to considering treatment on protocol.

When the patient is admitted to the Clinical Center for treatment, the PI, AI or designee, such as the medical staff fellow, will perform the consenting process.

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The informed consent form will contain all the Essential Elements of Informed Consent set forth in 21CFR, Part 50, the ICH Guideline for Good Clinical Practice, and the terms of the Declaration of Helsinki. Copies of the signed document should be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with Standard Operating Procedures.

9.6.1 Informed consent of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

10 DEVICE INFORMATION

10.1 LC BEAD LUMI™

(Also refer to the Investigational Brochure and the LUMI™ Bead Technical Dossier for complete information)

LC Bead LUMI™ consist of a macromer derived from a sulphonate modified polyvinyl alcohol (PVA) macromer and a sulphonated cross-linking agent (AMPS = 2-Acrylamido-2-methylpropane sulphonate, sodium salt), which contains a radiopaque moiety (triiodobenzyl

entity) that is covalently bound within the hydrogel structure. The radiopaque moiety is derived from triiodobenzyl aldehyde. The incorporation of this radiopaque moiety into the co-polymer imparts X-ray imageability by rendering the beads radiopaque.

Multiple sizes are available for the product LC Bead LUMI™. Glass vials in all size ranges will contain approximately 2ml of product in around 6 – 7 ml physiological buffered saline. The total volume in the vial is 8 - 9 ml. Each vial is provided sterile (SAL 10^{-6}) via moist heat sterilization and is only intended for single use.

The product is mixed with non-ionic contrast agent, such as Omnipaque™ (not included with the product) to help the physician / radiologist to evaluate the human vascular supply and in order to monitor the delivery of the product during the embolization procedure. LC Bead LUMI™ will be delivered using a typical microcatheter commercially available to the Interventional Radiologist community in 2.4 to 4 Fr (French size) ranges. The physician will use the product to administer the beads intra-arterially in order to physically block the target vessel.

LC Bead LUMI™ has been designed as a radiopaque version of the LC Bead™. Currently embolization with LC Bead ™ lacks post-procedural imaging feedback on exact bead location. The embolization process with LC Bead™ is monitored by detecting changes in antegrade flow of soluble iodinated contrast in which the beads are diluted. The embolization is continued until a desired embolization endpoint is reached. This process is completed without specific feedback on the bead location. In order to address this limitation, BTG has developed an imageable spherical embolic bead that can be visualized by X-ray based imaging (e.g., fluoroscopy and CT). The potential benefits envisaged for such a line extension are listed below:

- The radiopaque product will embolize the tumor feeding vessels, providing a marker for the location of the tumor.
- Areas of undertreatment may be detected and this may support the effective planning of additional interventions.
- The product may facilitate the follow-up of treated tumors by identifying previously treated regions.
- The introduction of imageability should allow physicians to identify areas of any undesirable non-target embolization.

10.1.1 Device design and performance specification

LC Bead LUMI™ has been designed to allow visualization of the bead product within the blood vessel by X-ray based imaging. The design control process considered the design inputs that were necessary to meet this key user requirement. A summary of the user requirements (archived in the Design History File) include device functionality, compatibility, sterility, packaging, clinical usability, shelf life and product disposal.

10.1.2 Preparation of LC Bead LUMI™

1. During preparation of LC Bead LUMI™, use controlled aseptic conditions.

2. Remove the plastic color coded flip cap from LC Bead LUMI™ vial but do not remove the metal ring around the stopper. With the spike of the ViaLok™ Vented Access Device centered to the rubber stopper of the vial, attach the device until the retention tabs snap on the LC Bead LUMI™ vial.

Note: The ViaLok™ Vented Access Device is not for direct infusion and should only be used for transfer of the beads into a syringe. The access device size corresponds to vial diameter and is intended for use with ISO-594 compatible mating luers. LC Bead LUMI™ has only been tested in conjunction with ViaLok™ Vented Access Device.

3. Remove and discard luer cap from the access device.

Note: To minimize risk of potential contamination, the ViaLok™ Vented Access Device protective cap shall remain attached to luer until accessed by the mating luer device.

4. Attach a 10ml syringe to the luer lock of the ViaLok™ Vented Access Device.

5. Invert vial and suspend the beads in solution by agitating in a swirling motion whilst drawing the LC Bead LUMI™ into the syringe.

6. Once all the solution is transferred discontinue the agitation and maintain the vial in the inverted position to allow the beads to settle in the syringe. Return only the clear solution to the vial and repeat previous step to recover remaining beads from the vial. This process may be repeated twice if required.

Note: Small traces of LC Bead LUMI™ may be retained in the vial.

7. Once LC Bead LUMI™ has settled at the bottom of the syringe; disconnect the syringe from the ViaLok™ Vented Access Device. Expel all packing solution to waste or suitable container, leaving only LC Bead LUMI™ within the syringe

8. LC Bead LUMI™ should be prepared for administration using 100% non-ionic contrast agent to obtain an optimum suspension. Please refer to Table 2 of the IFU (Appendix C, Section **0**) for recommended contrast agents.

9. Attach a connector to the syringe containing LC Bead LUMI™. Using a 20ml syringe take up 20ml of contrast agent and connect to the 10 ml syringe containing the LC Bead LUMI™.

10. Gently mix LC Bead LUMI™ and contrast agent between syringes through the connector, until a homogenous suspension is achieved.

11. Remove 20ml syringe and replace with 3ml syringe for delivery. Mix between the 10ml and 3ml syringes using a connector to obtain homogenous suspension of LC Bead LUMI™. After the contents of the 10ml syringe is delivered, the process can be repeated by transferring the remaining suspension from the 20ml syringe to the 10ml syringe through a connector.

Note: Please ensure mixing is performed between each refill of the 3ml syringe.

10.1.3 Delivery Instructions

Please note that LC Bead LUMI™ will settle quickly in some contrast agents. Prior to and during delivery ensure that the beads are in suspension. Please note that larger beads have shorter suspension times than the smaller size ranges of LC Bead LUMI™.

1. Using standard techniques, position the delivery catheter within the target vessel and the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of non-target vessels.

2. Use a 3ml syringe to manage the injection pressure during catheter delivery of the LC Bead LUMI™ beads.

3. Slowly inject LC Bead LUMI™ solution into the delivery catheter under x-ray techniques such as fluoroscopy, CBCT and CT imaging while observing the bead distribution to avoid reflux. If there is no effect on the antegrade flow rate, choose a larger size of LC Bead LUMI™ and repeat the delivery process. Exercise conservative judgment in determining the embolization endpoint.

4. Where necessary, saline flushes can be used to ensure full delivery of the LC Bead LUMI™.

5. Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge LC Bead LUMI™ that may still be within the catheter lumen.

6. Discard any open unused LC Bead LUMI™ as well as any other ancillary equipment used in the procedure such as the ViaLok™ Vented Access Device, syringes, needles, catheters, etc., following the applicable local standard practice.

10.1.4 Labeling

PACKAGE LABEL:

REF — Catalogue number

LOT — Batch number/Lot number

Do not reuse

Attention see instructions for use

STERILE — Steam Sterilized

Use-by date/Expiry

Protect from light/ Keep away from sunlight

Protect from moisture/ Keep dry

25°C / 2°C — Do not freeze. Store at 2-25°C.

Manufacturer

BTG

Patents
US 6,676,971; US 7,070,809, Other patents pending
Manufactured by:
Biocompatibles UK Ltd, a BTG International group company
Chapman House, Weydon Lane, Farnham, Surrey, GU9 8QL, United Kingdom
Tel: +44 (0)1252 732 732, Fax: +44 (0)1252 732 777
http://www.btg-im.com

LC Bead LUMI is a trademark of Biocompatibles UK Ltd, a BTG International group company. BTG and the BTG roundel logo are registered trademarks of BTG International Ltd.

10.1.5 Carton Label

Lot: XXXXXX Expiry: Yyyy-	510 (k) Clearance 152157 BTG-13-002 **(XXX-XXXµm)** **Unique Product ID:** 13002-001 to 13002-**XXX** **CAUTION** - Investigational device. Limited by Federal (US) law to investigational use. **Directions for Use**: See Protocol and Instructions for use.

mm	**Storage Conditions**: 2^{0}C – 25^{0}C ; Sterile, Do not re-use, Keep away from sunlight, Keep dry. Manufactured by Biocompatibles UK Ltd a BTG International group company, Chapman House, Weydon Lane, Farnham, Surrey GU9 8QL.

10.1.6 Vial Label

Lot: **XXXXXX** Expiry: **Yyyy-mm**	510 (k) Clearance 152157 BTG-13-002 **(XXX-XXXµm)** **Unique Product ID:** 13002-001 to 13002-**XXX** Manufactured by Biocompatibles UK Ltd a BTG International group company, Chapman House, Weydon Lane, Farnham, Surrey GU9 8QL.

11 REFERENCES

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12 APPENDICES

12.1 APPENDIX A: FDA 510 (K) CLEARANCE FOR LC BEAD LUMI

Biocompatibles UK Ltd
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BTG

14 December 2015

Bradford Wood, MD
NIH/DRD
10 Center Drive MSC 1182
Bethesda, MD 20892

Subject: FDA Clearance of LC Bead LUMI™

Dear Dr. Wood:

This letter is to inform you that LC Bead LUMI™ has been cleared by the FDA for commercial use and, therefore, commercial product will be available for the NIH Investigator Initiated study entitled "Pilot Study Using LC Bead LUMI Radio-opaque Embolic Beads to Detect and Characterize the Vascularity of Hepatic Tumors During Treatment with Transarterial Embolization (TAE) Alone or Combined with Thermal Ablation" upon provision of the NCI/NIH IRB approval, an IRB-approved protocol, and the IRB-approved Informed Consent. Enclosed is a copy of the FDA clearance letter.

Please send all documents to Jennifer Lubin by email to: Jennifer.Lubin@btgplc.com

Sincerely,

Carol Clark-Evans
Vice President, Regulatory Affairs

Enclosure
cc: J. Lubin

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

December 11, 2015

Biocompatibles UK Ltd.
% Robert Lally
Senior Vice President Regulatory Affairs
BTG International Inc.
Five Tower Bridge, Suite 800
300 Barr Harbor Drive
West Conshohocken, Pennsylvania 19428

Re: K152157
Trade/Device Name: LC Bead LUMI
Regulation Number: 21 CFR 870.3300
Regulation Name: Vascular Embolization Device
Regulatory Class: Class II
Product Code: KRD
Dated: October 29, 2015
Received: November 4, 2015

Dear Robert Lally:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in

the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Kenneth J. Cavanaugh -S

for

Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

12.2 APPENDIX C: LC BEAD LUMI™ RADIOPAQUE EMBOLIC BEAD INSTRUCTIONS FOR USE

LC Bead LUMI™ Radiopaque Embolic Bead

INSTRUCTIONS FOR USE
Version 2

STERILE: SINGLE USE ONLY:
(Do not use if package is opened or damaged)

DESCRIPTION:

LC Bead LUMI™ are precisely calibrated, radiopaque, biocompatible, non-resorbable hydrogel beads. The beads are produced from polyvinyl alcohol and contain a covalently bound radiopaque moiety.
LC Bead LUMI™ are manufactured to be inherently radiopaque and visible under imaging (Computed Tomography [CT], Cone Beam Computed Tomography [CBCT] and Fluoroscopy). LC Bead LUMI™ are available in four size ranges:

Size	Label Color
40-90µm	Orange
70-150µm	Black
100-300µm	Yellow
300-500µm	Blue

Table 1: Product size ranges for LC Bead LUMI™.

PRESENTATION:

- LC Bead LUMI™ are offered in a prefilled 10ml glass vial, stopper-sealed by an aluminium cap with a color-coded lid.
- Each vial contains approximately 2ml of product in sterile phosphate buffered saline. The total volume of LC Bead LUMI™ and sterile physiological saline is approximately 8ml.
- Each package contains a sterile 20mm ViaLok™ Vented Vial Access Device (Yukon Medical LLC, 4021 Stirrup Creek, Durham, NC USA) for removal of LC Bead LUMI™ from the vial.
- Each vial of LC Bead LUMI™ is intended for single patient use only. Do not re-sterilize. Discard any unused material.

INDICATIONS:

- LC Bead LUMI™ are intended to be used for the embolization of hypervascular tumors and arteriovenous malformations (AVM).

CONTRAINDICATIONS:

1. Patients intolerant to occlusion procedures.
2. Vascular anatomy or blood flow that precludes catheter placement or injection of embolics.
3. Presence or likely onset of vasospasm.
4. Presence or likely onset of hemorrhage.
5. Presence of severe atheromatous disease.
6. Lesion/tumor-feeding vessel with diameter smaller than any distal vessel(s) branching from it.
7. Presence of patent extra-to-intracranial anastomoses or shunts.
8. Presence of end arteries leading directly to cranial nerves.
9. Presence of arteries supplying the lesion/tumor not large enough to accept LC Bead LUMI™.
10. Vascular resistance peripheral to the feeding arteries precluding passage of LC Bead LUMI™ into the lesion/tumor.
11. Presence of collateral vessel pathways potentially endangering normal territories during the embolization procedure that cannot be coiled or blocked.
12. Presence of high-flow arteriovenous shunt with a diameter greater than the selected bead size that cannot be coiled or blocked.
13. Do not use LC Bead LUMI™ in the following applications:
    i. Embolization of arteriovenous (AV) shunts (i.e. where the blood does not pass through the arterial/capillary/venous transition but directly from artery to vein).
    ii. Any vasculature where LC Bead LUMI™ could pass directly into the internal carotid artery or other non-target territories.
    iii. Any neurovascular indication.
14. Do not use in the pulmonary arterial vasculature.

CAUTIONS:

- Embolization with LC Bead LUMI™ should only be performed by physicians who have received appropriate interventional occlusion training in the anatomical region intended to be embolized.
- Do not use if the vial or packaging appears damaged.
- Sterile and single-use product. Do not reuse due to risk of infection.
- If there are any symptoms of unwanted embolization during injection, consider stopping the procedure to evaluate the possibility of shunting. Such symptoms may include changes in patient's vital signs, such as hypoxia or central nervous system changes.
- In case of hypersensitivity to contrast agents it is recommended not to use LC Bead LUMI™.
- Consider upsizing LC Bead LUMI™ in the presence of AV shunts if angiographic evidence of embolization does not appear quickly during delivery.
- Use only the recommended non-ionic contrast agents (see Table 2).
- Non-target embolization may occur in the presence of arteriovenous anastomosis, branch vessels which lead away from the targeted embolization area, or emergent vessels not evident prior to embolization. The patient may experience severe complications as a result of non target embolization. Special care should be taken to avoid ischemia of non-tolerant, non-targeted tissue.
- Patients with prior biliary surgery, bile duct dilation or vessels close to bile ducts may be at increased risk from infection (e.g. biloma/ liver abscess).
- Consideration should be given to Tc99m-MAA scanning if there is suspicion of AV shunting, especially when using the smaller bead sizes.
- Risks of radiation from angiography and fluoroscopy used to visualise the blood vessels during embolization which may include a radiation burn and risks to future fertility.
- A maximum of 4 vials of LC Bead LUMI™ can be used in a single treatment session.

CAUTION:

Federal (USA) law restricts this device to sale by or on order of a physician.

POTENTIAL COMPLICATIONS:

1. Undesirable reflux or passage of LC Bead LUMI™ into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds, such as the pulmonary, internal carotid or coronary circulations.
2. Non-target embolization for example:
    - Pulmonary embolization
    - Pancreatitis
    - Deep vein thrombosis, or clotting of a deep vein in patient's leg(s)
    - Thrombosis of the artery at the incision site for arterial access
3. Ischemia at an undesirable location.
4. Capillary bed saturation and tissue damage.
5. Ischemic stroke or ischemic infarction.
6. Vessel or lesion/tumor rupture and hemorrhage.
7. Neurological deficits including cranial nerve palsies.
8. Vasospasm.
9. Recanalization.
10. Foreign body reactions necessitating medical intervention.
11. Infection necessitating medical intervention.
12. Clot formation at the tip of the catheter and subsequent dislodgement causing arterial thromboembolic sequelae.
13. Post embolization syndrome which may include nausea, fever, pain and increases in laboratory parameters such as elevated liver enzymes.
14. Allergic reactions to contrast agents or LC Bead LUMI™ in patients who are allergic or with known sensitivity to iodine / iodine containing substances.
15. Embolization of the wrong artery or migration of the beads to other parts of the body, which may necessitate further treatment.
16. Haematoma, or bruising or arterial aneurysm, at the arterial access incision site.
17. Liver abscess
18. Death.

CONSERVATION AND STORAGE:

- Unopened LC Bead LUMI™ must be stored between 2°C to 25°C, in a dry place in its original packaging. Protect the product from direct sun light. Use by the date indicated on the vial label.
- Once opened, LC Bead LUMI™ must be used within 4 hours if they are kept at room temperature or within 24 hours if they are stored in a refrigerator at 2-8°C.
- Do not freeze.

INSTRUCTIONS FOR USE:

- Select the size and quantity of LC Bead LUMI™ appropriate for the pathology and vasculature to be treated.
- Carefully evaluate the vascular network associated with the site to be embolized using high-resolution imaging prior to beginning the embolization procedure. Care should be taken to choose the appropriate size range of LC Bead LUMI™ that best matches the pathology (i.e. vascular target/vessel size/AVM nidus).
- When removing the vial from outer packaging visually inspect for breakage or sharp edges prior to use.
- Use appropriate protective clothing and hygiene measures.
- Choose a delivery catheter based on the size of the target vessel. Use the catheter's minimum inner diameter measurement to determine catheter-to-microsphere compatibility. Minimum catheter sizes are given in the table below.
- It is recommended to monitor the embolization procedure using X-ray imaging techniques such as CT, CBCT and fluoroscopy.
- Federal (USA) law restricts this device to sale by or on order of a physician.

PREPARATION AND DELIVERY OF LC BEAD LUMI™:

Note:
It is recommeneded to use non-ionic contrast agent during the delivery of LC Bead LUMI™. Throughout the preparation avoid the introduction of air bubbles. If air bubbles are observed, eliminate them to prevent potential aggregation of the beads.

Preparation of LC Bead LUMI™

1. During preparation of LC Bead LUMI™, use controlled aseptic conditions.
2. Remove the plastic color coded flip cap from LC Bead LUMI™ vial but do not remove the metal ring around the stopper. With the spike of the ViaLok™ Vented Access Device centred to the rubber stopper of the vial, attach the device until the retention tabs snap on the LC Bead LUMI™ vial.
   Note : The ViaLok™ Vented Access Device is not for direct infusion and should only be used for transfer of the beads into a syringe. The access device size corresponds to vial diameter and is intended for use with ISO-594 compatible mating luers. LC Bead LUMI™ has only been tested in conjunction with ViaLok™ Vented Access Device.
3. Remove and discard luer cap from the access device.
   Note: To minimise risk of potential contamination, the ViaLok™ Vented Access Device protective cap shall remain attached to luer until accessed by the mating luer device.
4. Attach a 10ml syringe to the luer lock of the ViaLok™ Vented Access Device.
5. Invert vial and suspend the beads in solution by agitiating in a swirling motion whilst drawing the LC Bead LUMI™ into the syringe.
6. Once all the solution is transferred discontinue the agitation and maintain the vial in the inverted position to allow the beads to settle in the syringe. Return only the clear solution to the vial and repeat previous step to recover remaining beads from the vial. This process may be repeated twice if required.
   Note:Small traces of LC Bead LUMI™ may be retained in the vial.
7. Once LC Bead LUMI™ has settled at the bottom of the syringe, disconnect the syringe from the ViaLok™ Vented Access Device. Expel all packing solution to waste or suitable container, leaving only LC Bead LUMI™ within the syringe
8. LC Bead LUMI™ should be prepared for administration using 100% non-ionic contrast agent to obtain an optimum suspension. Please refer to table 2 for recommended contrast agents..
9. Attach a connector to the syringe containing LC Bead LUMI™. Using a 20ml syringe take up 20ml of contrast agent and connect to the 10 ml syringe containing the LC Bead LUMI™.
10. Gently mix LC Bead LUMI™ and contrast agent between syringes through the connector, until a homogenous suspension is achieved. If desired, further dilution of bead to contrast agent may be perfomed using additional syringe and required contrast agent.
11. Remove 20ml syringe and replace with 3ml syringe for delivery. Mix between the 10ml and 3ml syringes using a connector to obtain homogenous suspension of LC Bead LUMI™. After the contents of the 10ml syringe is delivered, the process can be repeated by transferring the remaining suspension from the 20ml syringe to the 10ml syringe through a connector.
    Note: Please ensure mixing is performed between each refill of the 3ml syringe.

Recommended Catheters and Contrast Agents:
Once prepared, LC Bead LUMI™ has been tested and shown to be successfully delivered using the combinations of microsphere size, contrast medium and microcatheters shown in Table 2.

Product Size Range of LC Bead LUMI™	*Recommended Catheter (internal diameter)*	*Recommended Contrast Agents*
40-90µm (40-100µm)*	≥ 2.0 Fr (0.483mm / 0.019in)	Omnipaque 350 (Iohexol) Iomeron 400 (Iomeprol) Optiray 350 (Ioversol) Oxilan 350 (Ioxilan) Isovue 370 (Iopamidol) Ultravist 370 (Iopromide)
70-150µm (70-170µm)*	≥ 2.0 Fr (0.483mm / 0.019in)	
100-300µm (70-340µm)*	≥ 2.4 Fr (0.022in/ 0.54mm)	
300 – 500µm (250-550µm)*	≥ 4.0 Fr (0.041in/ 1.03mm)	

Notes:
- Other contrast agents have not been tested in conjunction with LC Bead LUMI™.
- Optiray 350, Oxilan 350, Isovue 370 and Ultravist 370 have not been tested for the 300-500µm size range
- Isovue 300 (Iopamidol) has been tested and is not recommended for use due the inadequate suspension times. Contrast agents of a similar or lower viscosity at 20°C should not be used with LC Bead LUMI™.
- *Potential bead size range based on manufacturers specification.

Table 2: Recommended catheter sizes and contrast agents for application with LC Bead LUMI™.

Delivery Instructions:

Note:
Please note that LC Bead LUMI™ will settle quickly in some contrast agents. Prior to and during delivery ensure that the beads are in suspension. Please note that larger beads have shorter suspension times than the smaller size ranges of LC Bead LUMI™.

1. Using standard techniques, position the delivery catheter within the target vessel and the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of non-target vessels.
2. Use a 3ml syringe to manage the injection pressure during catheter delivery of the LC Bead LUMI™ beads. Injection rate should balance the rate of forward flow in the blood vessel and the bead dilution in the syringe with a starting injection rate of approximately 1 cc/min of diluted LC Bead LUMI™ beads and contrast agent solution. The injection rate should be slower near the end of the procedure as the rate of forward flow in the embolized blood vessel decreases.
3. During any procedural delays or disruptions, the catheter should be cleared of LC Bead LUMI™ to prevent settling of beads and potentially leading to catheter blockages.
4. Slowly inject LC Bead LUMI™ solution into the delivery catheter under x-ray techniques such as fluoroscopy, CBCT and CT imaging while observing the bead distribution to avoid reflux. If there is no effect on the antegrade flow rate, choose a larger size of LC Bead LUMI™ and repeat the delivery process. Exercise conservative judgment in determining the embolization endpoint.
5. Where necessary, saline flushes can be used to ensure full delivery of the LC Bead LUMI™.
6. Upon completion of the treatment, remove the catheter while maintaining gentle suction so as not to dislodge LC Bead LUMI™ that may still be within the catheter lumen.
7. Discard any open unused LC Bead LUMI™ as well as any other ancillary equipment used in the procedure such as the ViaLok™ Vented Access Device, syringes, needles, catheters, etc, according to applicable local standard practice.

PACKAGE LABEL:

Catalogue number

Batch number/Lot number

Do not reuse

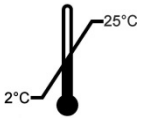
Attention see instructions for use

Steam Sterilized

Use-by date/Expiry

Protect from light/ Keep away from sunlight

Protect from moisture/ Keep dry



Do not freeze. Store at 2-25°C.

Manufacturer

Patents

US 6,652,883; US 6,676,971; US 7,070,809, Other patents pending

Manufactured by:

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