LC Bead LUMI for Prostatic Artery Embolization: A Pilot Study

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1.0 Introduction

1.1 Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB according to its policies and procedures.

1.2 Background

Over the past 5 years, data has emerged from numerous countries supporting the safety and efficacy of prostatic artery embolization (PAE) for the treatment of lower urinary tract symptoms (LUTS) in the setting of benign prostatic hyperplasia (BPH) (1). In response, the Food and Drug Administration (FDA) recently granted a de novo classification to Merit Medical Systems to expand the indications for Embosphere Microspheres to include PAE for the treatment of BPH. Moreover, it has given 510(k) clearance for Embozene Microspheres.

LC Bead LUMI is a spherical polyvinyl alcohol embolic particle that has become available for clinical use over the last two years. It is unique among embolic particles in that it is innately radiopaque. It is a reengineered iteration of LC Bead that now includes iodine moieties to provide radiopacity (2). A disadvantage of the new molecular structure is that it has a shorter suspension time and less compressibility (2). These factors can lead to clumping and sub-optimal proximal embolization.

While PAE is clinically effective in as many as 75% of patients at 2-year follow-up (3), there is still uncertainty as to the reasons for failure. Additionally, although they are rare, several major complications have occurred as a result of non-target embolization during PAE (1). Because LUMI is inherently radiopaque, its distribution can be imaged on post-embolization conventional or cone beam computed tomography (CT). If used for PAE, these scans could provide information about completeness of prostate embolization as well as the presence of non-target embolization, leading to improved embolization techniques and patient selection. Before these avenues can be investigated, it must be determined if PAE can be performed effectively and safely with LC Bead LUMI.

1.3 Medical Device

1.3.1 Name of Investigational Device

LC Bead LUMI (M0 or M1 bead sizes are acceptable for use in this trial)

1.3.2 Intended Use of the Investigational Device

LC Bead LUMI will be used for prostatic artery embolization in patients with BPH.

1.3.3 Description of the Investigational Device

LC Bead LUMI is a spherical polyvinyl alcohol embolic particle that incorporates radiopaque moieties (2). Once a catheter has been fluoroscopically guided into the target vessel, the beads are then injected, causing obstruction at the arteriole level

until the desired degree of embolization has occurred. We do not anticipate any changes in our use of the microspheres during the study.

1.4 Preclinical Data

LC Bead LUMI has undergone in vitro testing to evaluate its duration of suspension in solution, density in solution and deliverability through a catheter, as well as it degree of opacity on fluoroscopy and CT (2). In vivo testing in a rabbit VX2 tumor model demonstrated high visibility of the particles after embolization on fluoroscopy and cone beam CT (2). Similar in vivo testing was done in a swine model also demonstrating visibility under fluoroscopy and CT (4). Further swine liver model testing revealed that LC Bead LUMI is effective for embolization resulting in predictable ischemia/necrosis and excellent long-term biocompatibility (2).

1.5 Clinical Data to Date

There is no published data available for PAE with LC Bead LUMI. There is a case series reporting safe, successful use of LC Bead LUMI for the treatment of liver cancer in humans (5). There is also data supporting the safe and effective use of a closely related embolic (*Bead Block*-also a spherical polyvinyl alcohol embolic particle manufactured by BTG) for PAE (6).

1.6 Similar Approved Devices

To date there are 2 embolic devices that are approved for the indication of PAE, Embospheres and Embozene Microspheres. Embospheres was approved with a de novo classification request (see https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160040.pdf). Embozene Microspheres received 510(k) clearance (see https://www.accessdata.fda.gov/cdrh_docs/pdf18/K180102.pdf).

1.6.1 Safety and Efficacy of Embospheres

Based on a phase 3 multicenter clinical trial, the procedure using Embospheres was efficacious as 100% of subjects treated with PAE achieved a decrease of 3 or greater in IPSS. There were a total of 123 adverse event sin the PAE group, of which 86% were classified as mild. Serious adverse events in PAE patients were limited to urinary retention, sepsis, fever, UTI, rigors, and nausea in one patient each. A second study has included 2 patients at the time of the FDA filing. These 2 patients saw success in IPSS scores with no adverse events reported. A third trial also saw improvement in 4 patients at the time of FDA filing without any occurrence of reported adverse events.

A review of retrospective patient information for 286 patients also demonstrated efficacy of PAE with 97% of subjects demonstrating a reduction of IPSS of 3 or greater at 9-16 months. A total of 85% of total patients experience an adverse event with the majority being post-PAE syndrome, which is mild pain in the perineum, retropubic area, and/or urthra; fever; nausea (74.1%). Serious adverse events occurred in 1%.

1.6.2 Safety and Efficacy of Embozene Microspheres

Embozene is similar in size and material composition to Embospheres. This device also has similar indications for use. While there are some slight differences in the

two products, they do not affect the overall safety and efficacy of Embozene Microspheres.

Safety and efficacy was evaluated for Embozene Microspheres in a total of 38 patients that underwent PAE for the treatment of BPH in a prospective, single center study. Of these patients, 81.8% saw a reduction of at least 3 points of IPSS within 12 months. A total of 47% of patients demonstrated symptomatic improvement over baseline at 12 months. There was also evidence of a reduction in the size of the prostate following the PAE procedure. Overall, the study revealed a 100% success rate without incidence of non-targeted embolization. In regards to safety, the study revealed that PAE was safe as there was only an incidence of adverse events in 39.5% of patients, with no serious adverse events reported. The study did not report any incidence of post-PAE syndrome.

2.0 Study Objectives

The purpose of this pilot study is to determine preliminary estimates of the parameters related to the distribution of the study endpoints including: IPSS and QoL score changes, Qmax changes, PVR changes, percent prostate infarction and presence of non-target embolization.

3.0 Study Design

3.1 General Design

This will be an open label pilot study with a small population undergoing an intervention to determine initial safety and potential for efficacy as measured by improvement of LUTS and decrease in prostate size

3.2 Primary Study Endpoint

Reduction in IPSS at 6 months

3.3 Secondary Study Endpoints

1. Improvement of QoL score at 6 months
2. Improvement of uroflowmetry (Qmax, PVR) at 6 months
3. Reduction of prostate volume at 6 months
4. Percentage of prostate infarcted at 6 months
5. Incidence of non-target embolization at 6 months
6. Incidence of minor complications at 6 months
7. Improvement in IIEF at 6 months

3.4 Primary Safety Endpoints

1. Incidence and classification of major device related complications using Clavien-Dindo classification system at 6 months

3.5 Secondary Safety Endpoints

1. Incidence and classification of minor device related complications using Clavien-Dindo classification system at 6 months

4.0 Subject Selection and Withdrawal

4.1 General Characteristics of the Proposed Subject Population

Study subjects will be men with moderate severe LUTS refractory to medication with measured prostate gland size >50 grams.

4.2 Anticipated Number of Research Subjects

Enrollment into the investigation will be defined as providing informed consent for study participation per IRB policies.

Twenty subjects will be enrolled and all are anticipated to complete the study.

4.3 Inclusion Criteria

1. Male
2. Age > 40
3. Prostate gland >50 grams as measured by pre-procedural CT
4. Have previously taken BPH medication for 6 months without desired improvement of LUTS or has started medication and stopped due to unwanted side effects
5. Moderate to severe LUTS as defined by IPSS score >18
6. Peak urine flow rate (Qmax) <12 ml/sec
7. Capable of giving informed consent
8. Life expectancy greater than 1 year

4.4 Exclusion Criteria

1. Severe vascular disease
2. Uncontrolled diabetes mellitus
3. Immunosuppression
4. Neurogenic bladder and/or sphincter abnormalities secondary to Parkinson's disease, multiple sclerosis, cerebral vascular accident, diabetes, etc.
5. Complete urinary retention
6. Impaired kidney function (serum creatinine level > 1.8 mg/dl or a glomerular filtration rate < 60 as approximated using serum creatinine levels) unless anuric and on dialysis.
7. Confirmed or suspected bladder cancer
8. Urethral strictures, bladder neck contracture, or other potentially confounding bladder pathology
9. Ongoing urogenital infection
10. Previous pelvic radiation or radical pelvic surgery
11. Confirmed or suspected malignancy of the prostate based on DRE, TRUS or PSA (> 10 ng/ml or > 4.0 ng/ml and < 10 ng/ml with free PSA < 25% of total PSA without a negative biopsy).
12. Uncorrectable coagulopathy including INR > 1.5 or platelets < 50,000
13. Contrast hypersensitivity refractory to standard medications (antihistamines, steroids)

4.5 Subject Recruitment and Screening

Subjects will be recruited from the urology and vascular & interventional clinics at the University of North Carolina Hospital as well as at outlying clinics staffed by UNC Urology. A second site, Vascular Institute of Virginia, will also recruit patients from interventional radiology and urology clinics in the Northern Virginia Area.

4.6 Early Withdrawal of Subjects

4.6.1 Criteria for Removal from Study

Subjects will be withdrawn from the study if a major complication occurs that prevents completion of PAE or the ability to complete the follow up visits. Patients may also withdraw at any point at their discretion. Data will be included with an intent to treat analysis. Reasons for study withdrawal will be recorded.

4.6.2 Follow-up for Withdrawn Subjects

If a subject withdraws from the study, any recorded data will still be included in the analysis. Subjects will only be replaced if they withdrew prior to undergoing PAE.

5.0 Study Treatment or Diagnostic Product Procedures

5.1 Description

Subjects will be advised to stop taking their BPH medications two weeks prior to PAE. Though this is advised, it is not required if they cannot tolerate cessation. They will be given a dose of antibiotics on the day of the procedure and continue with oral antibiotics for seven days after the procedure. Additionally, non-steroidal anti-inflammatory medication will be administered mid-procedure. The patients will be given the choice of receiving intravenous anxiolytic and analgesic medication during procedure or proceeding with local anesthetic only.

Ultrasound-guided access into common femoral artery or radial artery will be obtained. An intra-arterial sheath will be placed. Through this sheath a diagnostic catheter will be used to perform pelvic angiography. Based on these images and CT angiography obtained before the procedure, a microcatheter will be fluoroscopically guided into the prostatic artery. LC Bead LUMI will then be injected under fluoroscopic guidance to prevent reflux and non-target embolization. Injection will continue until there is stasis. The catheter will then be guided into the contralateral prostatic artery and repeat embolization will be performed until stasis. If necessary, extraprostatic arterial anastomoses will be embolized with a coil or a gel-foam pledget to protect against non-target embolization. The catheter and sheath will then be removed and hemostasis will be achieved with compression or an intra-arterial closure device. The subject subsequently will be discharged home the same day or the following day.

It is anticipated that less than 4 milliliters of LC Bead LUMI will be required for bilateral embolization. LC Bead LUMI currently have FDA approval for embolization of hypervascular tumors and arterio-venous malformations.

5.2 Method for Assigning Subject to Treatment Groups

Because this is a pilot study to assess feasibility, all subjects will receive the study intervention (PAE).

5.3 Subject Compliance Monitoring

Study coordinators and physicians will inquire of the subjects to determine when they have stopped taking their BPH medications prior to the procedure. Additionally, the subjects will be asked if they completed all seven days of their post-procedural antibiotic regimen.

5.4 Prior and Concomitant Therapy

The subjects will be required to have been on medical therapy for BPH for at least six months prior to undergoing PAE. They will be advised to stop the BPH medications two weeks prior to undergoing PAE. They will be asked to discontinue BPH medication after PAE. Some patients may require maintenance of their BPH medications pending alternative therapy. Such medications include prescription and over-the-counter drugs. If potentially confounding medications are clinically appropriate to be taken concurrent with the study, dosage should not change during the study period unless medically necessary.

5.5 Blinding of Study

As a pilot study to assess feasibility, all subjects will receive PAE. Therefore, neither the study physicians nor patients will be blinded to the treatment protocol.

5.6 Receiving, Storage, Dispensing and Return

5.6.1 Receipt of Investigational Device Supplies

LC Bead LUMI will be stored within the Vascular and Interventional Radiology procedural suite.

5.6.2 Storage

LC Bead LUMI must be stored in a cool, dark, dry place in their original packing.

5.6.3 Dispensing

LC Bead LUMI are routinely used in VIR. No study specific dispensing techniques will be used.

5.6.4 Return or Destruction of Investigational Device

The Institution and Sponsor-Investigator shall, return any such Product to Company promptly if requested by the Company upon the completion or termination of the Study for which such Product was being utilized, or promptly dispose of or destroy, as the Company may reasonably direct, all of its remaining stocks of Product. Risk of loss to any such Product shall reside with the Institution. Institution shall reimburse Company for any loss of or damage to any Product provided by Company under this Agreement due to the negligence of Institution or Sponsor-Investigator, ordinary wear and tear excepted. The Institution and Sponsor-Investigator shall not use any Product provided by Company under this Agreement for any purpose whatsoever except as is necessary for the conduct of the Study.

6.0 Study Procedures

6.1 Pre-Study Visit

Possible enrollees will have already undergone a standard TURP/OP work-up, which typically includes a history, physical exam, urine flow rate recording (Qmax), post-void residual urine volume assessment (PVR), and imaging to measure prostate size. These workups also generally include the following laboratory testing-- UA, PSA, CBC, INR, and chemistry.

6.2 Visit 1 (Vascular Interventional Radiology Clinic)

If a patient qualifies to be a subject in the study based on the inclusion and exclusion criteria listed in section 4.3 and 4.4, the study coordinator will be notified. The coordinator will review the study with the patient and obtain written informed consent. Once the subject is enrolled in the study, he will be seen by one of the co-investigators in either UNC or VIV IR clinic. The procedure will be again described to the patient and any questions will be answered. International Prostate Symptoms Survey (IPSS), International Index of Erectile Function (IIEF) and Quality of Life (QOL) questionnaires will be completed if not done during the pre-study work-up. A CT of the pelvis without contrast will be ordered and obtained prior to visit 2 for baseline evaluation of the prostate unless the patient has one from the prior 6 months. If the patient had a CT of the pelvis within the past 6 months, this CT will be used.

6.3 Visit 2 (PAE)

PAE will be performed as described in part 5.1 above within 4 weeks of Visit 1. The day following the procedure, the subject will be contacted by telephone to inquire about symptoms that could be the result of the procedure. In addition, they will be given a pager number to reach a physician 24 hours a day to report any adverse symptoms and receive medical advice.

6.4 Visit 3 (1 Day Follow Up)

Subjects will be contacted by study personnel the day after PAE to inquire about delayed onset complications.

6.5 Visit 4 (3 Month Follow-Up)

Subjects will return 90 +/- 7 days after PAE to complete IPSS, IIEF, and QOL questionnaires; to have Qmax and PVR measured; and to have a follow up CT of the pelvis to evaluate for non-target embolization and PV changes as well as percent prostate infarction.

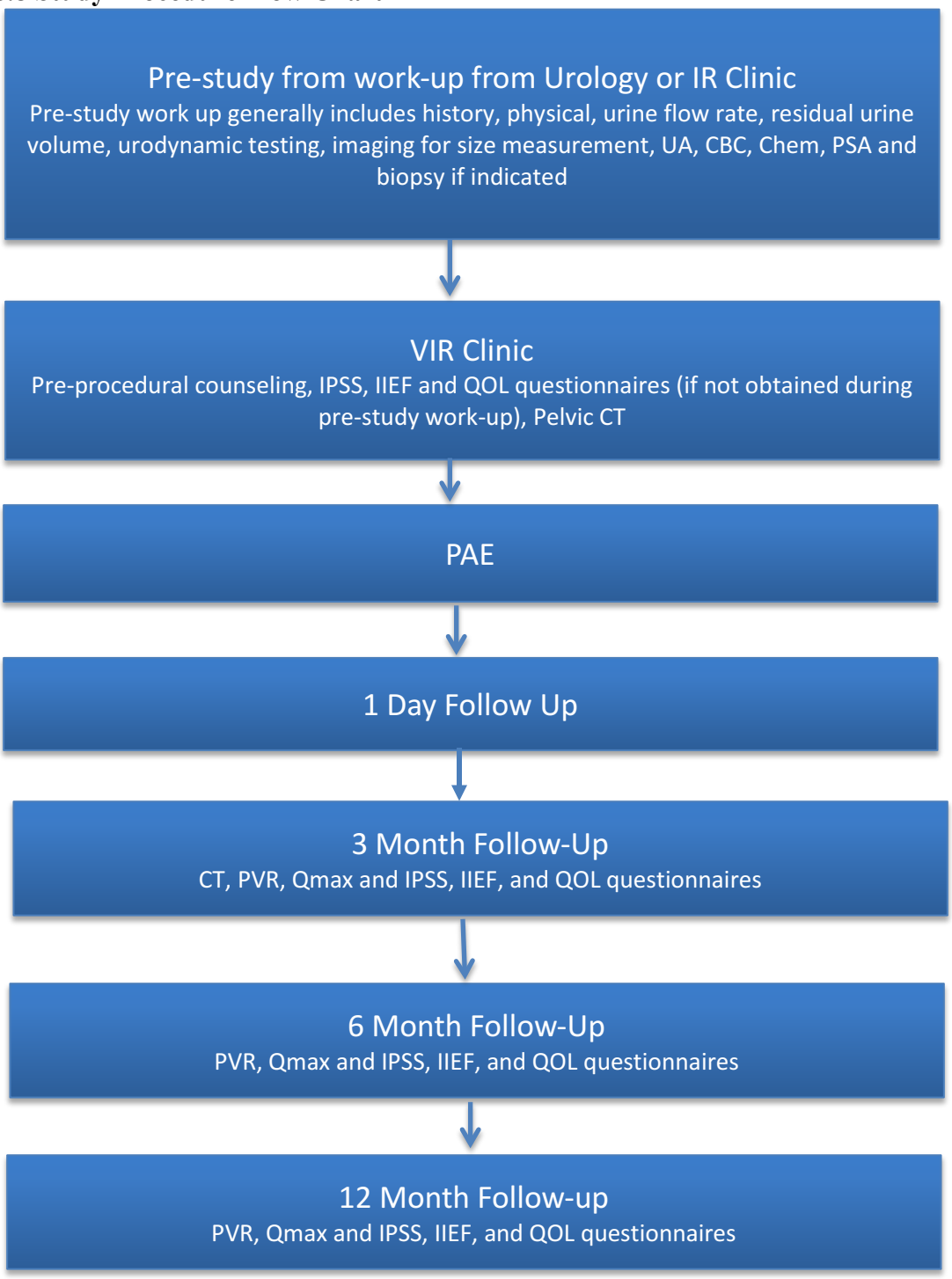
6.6 Visit 5 (6 Month Follow-Up)

Subjects will return 180 +/- 7 days after PAE to complete IPSS, IIEF, and QOL questionnaires and to have Qmax and PVR measured.

6.7 Visit 6 (12 Month Follow-Up)

Subjects will return 360 days +/- 14 days after PAE to complete IPSS, IIEF, and QOL questionnaires and to have Qmax and PVR measured.

6.8 Study Procedure Flow Chart



7.0 Safety and Effectiveness Assessments

7.1 Safety Assessments

Subjects will be observed for several hours after PAE to monitor for immediate complications to include bleeding, infection and acute ischemia of the rectum and bladder. Subjects will be contacted by study personnel the day after PAE to inquire about delayed onset complications. The subjects will also be given a phone number that they can call to reach a nurse if they believe they have developed a complication of the procedure.

7.2 Effectiveness Assessments

Technical success will be defined as bilateral prostatic artery embolization. This will be determined during the procedure. Clinical success will be defined by a reduction of IPSS of $\geq 25\%$ and reduction of QoL by ≥ 2 . The size of the prostate will be measured by CT at 3 the follow-up visit. IPSS, QoL, IIEF, PVR and Qmax will be measured at 3, 6 and 12-month follow-ups.

8.0 Statistical Plan

8.1 Sample Size Determination

Twenty subjects will be enrolled into this pilot study. Because there is no previous study reporting results for PAE with LC Bead LUMI, this pilot study will provide sample size data for a larger trial with adequate power. Due to budgetary constraints, we have selected a sample size of 20 participants. Given our sample size, and using parameters determined from prior studies, we expect to have 3.60% precision for the estimate of percent change in IPSS score from baseline to 6 month follow-up.(1)

8.2 Statistical Methods

Fractions and percentages will be used to describe technical and clinical success rates as well as major, minor and specific complication rates. Descriptive statistics including means and standard deviations will be used to summarize both discrete questionnaire scores and continuous values for prostate size, Qmax, and PVR for the 3-12 month follow-up period. Prostate size is only measured before the procedure and 3 months after the procedure. Percent change will be calculated between the baseline and final values. Continuous measures will be described using 95% confidence intervals. Feasibility for a future trial will be assessed using retention rates at each visit. Retention rates will be used to plan sample sizes for future studies.

Any deviations from the previously described statistical plan will be described and justified in a protocol amendment and/or in the final report submitted to the IDE application.

8.3 Subject Population(s) for Analysis

All subjects' data will be included for analysis even if follow up data is incomplete. Every attempt will be made to ensure that there is as little missing data as possible including reminder phone calls and follow-up phone calls if a subject misses a visit.

8.4 Interim Analysis

No interim analysis is planned.

9.0 Risk Analysis

9.1 Anticipated Risks

A recent meta-analysis of PAE data from 662 patients in nine studies reported only two major complication (0.3% major complication rate) involving bladder ischemia requiring surgery and severe urinary sepsis requiring hospitalization. Among minor complications transient rectalgia and/or dysuria (9.1%), acute urinary rentention (7.9%) and transient hematuria (4.4%) were the most common (1).

9.2 Adverse Event Definitions

Adverse events, Serious Adverse Events and Product Malfunctions

An adverse event (AE) is defined as any untoward or unfavourable medical occurrence in a human patient or clinical trial subject administered a medicinal product, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the patient's participation in the research, and which does not necessarily have a causal relationship with this treatment (study medication, application of the study device, etc.) or study participation. It includes all adverse events regardless of seriousness or relatedness.

A serious adverse event (SAE) is defined as an adverse event that

a) Results in death
b) Led to a serious deterioration in health that either:
   I. Results in a life-threatening illness or injury, or
   II. Results in a permanent impairment of a body structure or a body function, or
   III. Requires in-patient hospitalization or prolongation of existing hospitalization, or
   IV. Results in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
   V. Results in a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
c) Led to fetal distress, foetal death or a congenital abnormality or birth defect

A product malfunction is defined as a failure of the device to meet its performance specifications, essential function or otherwise perform as intended. Performance specifications include all claims made in the labelling for the device. The essential function of a device refers not only to the device's labelled use, but for any use widely prescribed within the practice of medicine.

Reporting of Adverse Events, Serious Adverse Events and Device Malfunctions

The Institution and/or the Sponsor-Investigator shall report all and any serious adverse events, product malfunctions or quality complaints (regardless of causality) that they become aware of in relation to the Product and/or the investigation to BTG.

All reports will be exchanged in English and Sponsor-Investigator will also provide BTG with such information and reasonable assistance as may be requested by BTG to allow BTG to comply with their obligations.

The Institution and/or the Sponsor-Investigator shall report all SAEs and incidents impacting patient safety to pharmacovigilance@btgplc.com.

SAEs

The Sponsor-Investigator will report SAEs within **one business day** to enable BTG to comply with their obligations as the device manufacturer, under applicable laws and regulations.

All reports will contain the following, if available:

- Study title and name of the Sponsor-Investigator.
- Patient number
- Adverse event number
- Date of event occurrence/date notified
- Product details
    - Product name/ part number
    - Size / dose
    - Batch / lot number
- Adverse event details along with comprehensive event description
- Action(s) taken to treat or resolve the event
- Outcome
- Investigators opinion of causality of event i.e. related to
    - Drug
    - Device
    - Procedure
- Product returned to BTG if applicable

Device Malfunctions

The Institution and/or the Sponsor-Investigator shall report all device malfunctions and/or quality complaints to within one business day of becoming aware of the issue.

9.3 Recording of Adverse Events

Research subjects will be questioned about adverse effects by telephone the day following the procedure. In addition they will be given a pager number to reach a physician 24 hours a day to report adverse effects and receive medical advice. The subjects will also be questioned about possible adverse effects at each follow-up visit.

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

An abnormal test finding will be classified as an *adverse effect* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms

- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
    - Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.
- The test finding leads to a change in study protocol or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse effect by the Sponsor-Investigator.

9.4 Causality and severity assessment

The investigator-sponsor will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and 3) if the adverse effect meets the criteria for a *serious adverse effect*.

If the investigator-sponsor's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)", the adverse effect will be classified as *associated with the use of the investigational device or study treatment or diagnostic drug product(s)* for reporting purposes. If the investigator-sponsor's final determination of causality is "unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

9.5 Reporting of Adverse Effects and Unanticipated Problems

9.5.1 Reporting of adverse reactions to the FDA

The investigator-sponsor will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an *unanticipated adverse device effect. A* copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and in no event, later than 10 working days after the investigator-sponsor first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an *unanticipated adverse device effect* does, in fact, meet the requirements for reporting; the investigator-sponsor will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the investigator-sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

9.5.2 Reporting Adverse Events to the Responsible IRB

In accordance with applicable policies of the University of North Carolina Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or volunteered adverse effect that is determined to be (1) unexpected; (2) related or possibly related to the research; and (3) involves increased or greater risk of harm to participant(s) or others than was previously known or approved by the IRB. Adverse effect reports will be submitted to the IRB in accordance with the IRB policies and procedures.

9.6 Stopping Rules

The study will be stopped if there is greater than one major complication as defined by the Society of Interventional Radiology Classification System for Complications by Outcome (7).

9.7 Medical Monitoring

9.7.1 Data and Safety Monitoring Plan

Safety Monitoring will be performed by a licensed physician who is not a study investigator. The CRFs and any relevant source documents will be sent to the medical safety monitor (as above) who will review them after treatment is complete for subject 1, 5, 10 and 20.

Complications will be assessed by the PI, categorized into major and minor categories and recorded on the CRF. CRFs and appropriate source documents will be made available to this individual for bi-monthly (every 2 months) review to ensure completeness of data collection. Any discrepancies will be immediately addressed by the PI. All adverse events will be recorded and then summarized for inclusion in the final manuscript.

Data monitoring will be performed by an individual who is not a study investigator. CRFs and appropriate source documents will be made available to this individual for bi-monthly review to ensure completeness of data collection. Any discrepancies will be immediately addressed by the PI.

9.7.2 Data and Safety Monitoring Board

Because this is a pilot study with only 20 subjects, no DSMB will be used for this study. Data and safety monitoring will be conducted by individuals who are not investigators on this study.

10.0.1 Data Handling and Record Keeping

10.1Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Consistent with these regulations a signed authorization will be obtained that informs each subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Copies of completed CRFs with subject IDs will be scanned and sent to the lead study coordinator at UNC for entry in the study database. CRFs should be sent within 5 business days to ensure timely entry.

10.3 Case Report Forms

The case report forms will be collected by the principal investigator and will be reviewed monthly for accuracy and completion.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

The coordinator at each site will complete the first CRF together with one of the Co-PIs to verify that it is completed correctly. Then, we will verify a randomly selected 25% of all source docs at the conclusion of data collection. Randomization will occur on a visit level and not per patient. The randomization for this verification will be generated using a random number generator in Excel.

10.4 Record Retention

It is the investigator's responsibility to retain study essential documents during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Research records and original signed consent forms are to be retained by principal investigator for at least 6 years if the form includes authorization for use of private health information. Investigators may need to retain these documents for a longer period if required by an agreement with a sponsor or per other applicable regulatory requirements. The 6 year minimum retention of authorizations complies with the privacy regulation requirements.

10.5 IRB Documentation

The principal investigator and research coordinator will be responsible for maintaining IRB correspondence. IRB approved forms maintained as part of the study will include the subject consent form and the HIPAA authorization form.

11.0 Study Monitoring, Auditing and Inspecting

11.1 Study Monitoring Plan

11.1.1 Locations

Initial enrollment will occur at a UNC Urology clinic (within the main hospital or off-site) or at VIR clinic within the main hospital. PAE will be performed within the VIR department of UNC Hospital, a facility that has an on-call emergency response team, an emergency department, intensive care units and a full surgical operating suite. Follow up imaging, tests and questionnaires will occur in UNC Hospital.

11.1.2 Study Staff Responsibilities and Training

CITI Training:

The investigators and all staff involved in the study will have completed their required Collaborative IRB Training Initiative (CITI) in the protection of human research subjects and Good Clinical Practice training.

Drs. Isaacson or Bagla (all fellowship trained interventional radiologists) will be the only primary operators for each of the PAE's. Dr. Isaacson has performed approximately 400 arterial embolization procedures with 190 prior PAEs. Dr. Bagla has performed approximately 900 arterial embolization procedures with approximately 350 prior PAEs.

Dr. Raynor (board certified urologists) will oversee urologic work-up of potential subjects as well as urologic care of any AEs requiring treatment.

11.1.3 Quality Assurance and Quality Control

The research coordinator will monitor the study files on a monthly basis to ensure the appropriate regulatory and IRB documentations are on file and up to date. The research coordinator will also be responsible for ensuring proper study documentation in order to verify compliance with Institutional policy, IRB, FDA and GCP guidelines in the following areas: Informed consent, Protocol, Source Documents and Electronic Case Report Forms.

11.1.4 Safety Monitoring

The research coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or medical monitor of all Unanticipated Problems/SAE's.

The research coordinator and Principal Investigator will confirm that all Adverse effects (AE) are correctly entered into the AE log by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; notify the IRB and FDA of all Unanticipated Problems/SAEs and AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who not investigator on the research and acting as a safety monitor for the study.

The research coordinator will confirm that the AEs are correctly entered into the AE log. The Monitor will confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies, as required.

11.1.5 Monitoring Activities

A safety monitor who is not a study investigator will conduct bimonthly safety monitoring. Adverse events will be documented and reported as described above.

The following issues will be addressed quarterly or more frequently as necessary:

- Verify receipt of all documents and supplies needed to conduct study
- Informed consent obtained for each participant
- CRF completion
- Investigational product accountability
- Check and review of the regulatory binder and all essential documents
- Clinical supply inventory
- SAE reporting
- Enrollment issues and targets
- Protocol amendment and their approval by the IRB
- Significant protocol deviations
- Personnel changes
- Updated regulatory documentation
- Any other issue as deemed important to the conduct of the study

11.1.6 Study Closure

Upon study closure a final evaluation of the data will ensure that all forms are present and complete. The data, scanned copies of the consent forms and questionnaires and all IRB correspondence will be maintained in digitally secure location under the supervision of the research coordinator. Any paper copies will be shredded. All subjects will be contacted via phone to thank them for their participation and to discuss the study findings as well possible additional treatment options.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Research Quality Assurance Office, IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

12.0 Ethics

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, the relevant federal regulations, and IRB policies and procedures and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB according to its policies and procedures.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of all subjects will be sought using the IRB-approved consent form. Before a subject undergoes any study procedure, an informed consent discussion will be conducted and written informed consent obtained with a consent form signed by the subject or legally acceptable surrogate if applicable. An investigator-designated research professional will obtain written informed consent from subjects. All subjects will be given a signed copy of the informed consent form.

13.0 Study Finances

13.1 Funding Source

This study is funded by a grant from Biocompatibles, UK LTD.

13.2 Conflict of Interest

Any investigator who has a conflict of interest (COI) with this study as defined by the policies of the University of North Carolina will have the conflict reviewed by a properly constituted Conflict of Interest Review Committee with a committee-sanctioned conflict management plan that has been reviewed and approved by the IRB prior to participation in this study. All University of North Carolina investigators will follow the University conflict of interest policy.

13.3 Subject Stipends or Travel Reimbursements

Subjects be reimbursed for travel/parking expenses as well as for their time during study visits.

14.0 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study will be obligated to provide the sponsor with complete test results and all data derived from the study.

15.0 References

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16.0 Appendices

Figure 1. Time and Events Table

TIME TABLE	Pre-Study Standard of Care	Visit 1	Visit 2	Visit 3 (3 month follow-up)	Visit 4 (6 month follow-up)	Visit 5 (12 month follow-up)
History and Physical Exam	X					
Qmax	X			X	X	X
PVR	X			X	X	X
Prostate volume measurement	X			X		
PSA	X					
PAE			X			
IPSS questionnaire		X		X	X	X
IIEF questionnaire		X		X	X	X
QOL questionnaire		X		X	X	X
CT		X		X		

Figure 2. Study Device (LC Bead LUMI)