Geniculate Artery Embolization for the Treatment of Knee Pain Secondary to Osteoarthritis

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Protocol Title:	**Geniculate Artery Embolization for the Treatment of Knee Pain Secondary to Osteoarthritis**
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Medical Device:	Embozene Microspheres
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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

Osteoarthritis (OA) is a common and major cause of pain and disability. An estimated 26.9 million adults in the US suffer from OA (1) and nearly 50% of adults may develop symptomatic knee OA by age 85 (2). Knee OA affects obese individuals at a higher rate with ⅔ of individuals developing symptomatic disease. The treatment for knee osteoarthritis is broad and includes: exercise and patient education; pharmacologic therapies, including oral, topical, and intra-articular medications; and surgical interventions, including total joint arthroplasty. Minor symptoms can be managed with non-opioid pain medications such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), which are the mainstay of pain management for OA. Severe and end- stage osteoarthritis can be treated with total joint arthroplasty. Unfortunately, NSAIDs can be a cause of renal failure, exacerbation of asthma and most notably, gastrointestinal hemorrhage. Estimated number of deaths from NSAID-related gastrointestinal bleeding has been estimated at 16500 (3). With the significant morbidity associated with treatment of OA, there is a need to develop a new, effective, minimally invasive and safe treatment for pain related to osteoarthritis of the knee.

The principal symptom of OA, pain, is mediated by a number of factors. However, angiogenesis resulting in neovascularity, neural sensitization and inflammation has been described as a potential pathophysiological pathway of the deep joint pain described by many OA patients (4, 5). This increased vascularity in the setting of pain and OA has been the focus of recent endovascular investigation, with the proposed mechanism of embolization as a novel treatment.

Particulate embolization of geniculate artery branches supplying hypervascular joint tissue, the same technique we are proposing to treat pain from OA, has been previously described as a safe treatment for hemorrhage after total knee arthroplasty in multiple reports (6-9). In 2008, three cases were reported using 150-355 micrometer particles without any complications (6). In 2013, a Japanese group reported the use of 1000-2000 micrometer particles in the treatment of five patients, again without complication (9). In 2015, an author group that includes one of the Co-PIs reported outcomes from 13 cases in which there were no major complications and two minor complications (transient cutaneous ischemia) (8). Finally, in 2016 a fourth report of 14 embolizations was published in which there were no major complications and, again, two minor complications (transient cutaneous ischemia) (7).

Embolization of hypervascular joint tissue for the treatment of pain has been pioneered by Dr. Okuna and his colleagues in Japan. They initially reported a case series in which they were able to reduce pain related to refractory tendinopathy and enthesopathy in multiple joints in 7 patients using an antibiotic particulate for embolization without major complication (10). Subsequently, the same team published its experience with transcatheter embolization of hypervascular tissue within the shoulder joint in 7 patients diagnosed with adhesive capsulitis. The procedure successfully resulted in pain reduction with any complications (11). Finally, Okuno et al also published their results after synovial embolization in patients with painful OA. The procedure was performed on 14 patients and there were no major complications. There was significant pain reduction and decreased difficulty of movement at 4 months. Medication frequency also decreased after embolization (12).

The current investigation teams have led efforts pioneering embolization procedures in novel targets that have proved successful (13-18). We have also had experience in embolization of the knee, in particular with post-arthroplasty hemorrhage (8). With our proven experience in embolization, and in particular the local-regional anatomy, we have set forth to pursue a US study evaluating embolization as a treatment for OA related knee pain.

1.3 Medical Device

1.3.1 Name of Investigational Device

Embozene Microspheres

1.3.2 Intended Use of the Investigational Device

Embozene Microspheres will be used for geniculate artery embolization (GAE) in subjects with knee osteoarthritis.

1.3.3 Description of the Investigational Device

CeloNova BioSciences Inc. Embozene® Microspheres and Embozene® Color Advanced Microspheres were found to be substantially equivalent and cleared medical devices (Premarket Notification K073417) to prior technologies:

- Boston Scientific Contours SE ™ Microspheres (K032707), and
- Biocompatible Bead Block ™ Microspheres (K033761).

Identified in the Code of Federal Regulations 21 Part 870- Subpart D-Cardiovascular Prosthetic Devices.

Classification Name: Artificial Embolization Device. Class II Medical Device Common Name: Vascular Embolization Device Subpart D-Prosthetic Devices; Sec. 870.3300

Indication for Use: A vascular embolization device is an intravascular implant intended to control hemorrhaging due to aneurysms, certain types of tumors (e.g.,

nephroma, hepatoma, uterine fibroids), and arteriovenous malformations. This does not include cyanoacrylates and other embolic agents, which act by polymerization or precipitation. Embolization devices used in neurovascular applications are also not included in this classification.

Embozene Microspheres are tightly calibrated, sub-millimeter, hydrogel beads coated with inorganic perfluorinated polymer coating for biocompatibility. They are manufactured in multiple sub-millimeter sizes. They come in a liquid suspension that is mixed with iodinated contrast before use. Once a catheter has been fluoroscopically guided into the target vessel, the microspheres are then injected, causing obstruction at the arteriole level until the desired degree of embolization has occurred. The microspheres used during the study will be unchanged.

1.4 Preclinical Data

Embozene Microspheres have proven to be an effective embolization material with high biocompatibility in multiple non-human studies (19-23). In porcine model studies, Embozene Microspheres effectively embolized renal arteries without toxicity, with low immunoreactivity and associated inflammation of the surrounding tissue and with low rates of recanalization. Inflammation within porcine liver models was also seen to be low after Embozene embolization.

1.5 Clinical Data to Date

Embozene Microspheres have been safely used as an embolic agent to target hypervascular lesions throughout the body including hepatocellular carcinoma, meningioma, uterine fibroids and adenomyosis and benign prostatic hyperplasia (18, 24-26). The investigators have also performed GAE for knee hemarthrosis with technical and clinical success using Embozene Microspheres (8). Recently, Embozene has been used safely and effectively for GAE to treat medial knee pain in the setting of osteoarthritis (12). Embozene Microspheres are FDA approved for the treatment of arteriovenous malformations and hypervascular tumors.

2.0 Study Objectives

The primary aims of this study are to determine if GAE will reduce the severity of pain as well as global disability (resulting from the combination of pain, stiffness and difficulty performing daily activities) caused by knee OA and if it can be performed safely. The secondary aim is to determine if GAE can result in the decreased necessity for ongoing conservative OA therapies such as medication therapy and joint injections. Another secondary aim to provide 'sample size data' for planning a future study.

3.0 Study Design

3.1 General Design

This will be an open label pilot study with a small population undergoing GAE to determine safety and efficacy. After IRB approval of a written informed consent and over, approximately a 24 month duration, N=20 subjects will be recruited within 2 hospital clinic based settings. Only subjects ≥ 40 years will be screened for study recruitment and will be un-blinded from study treatment. Clinical procedures and

evaluations will consist of a preoperative screening assessment to determine if the potential study subject meets the inclusion and exclusion criteria, enrollment, surgical procedure for geniculate artery embolization, and follow-up visits at 24 hours, 1, 3 & 6 months. An MRI will be performed at the 1-month visit to detect a change in synovial vascularity and to exclude complication.

3.2 Primary Study Endpoints

1. Overall efficacy of treatment as determined by a minimal clinically significant reduction in global Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire scoring of 16% (27) at 6 months follow-up.
2. Minimal clinically important decrease of 15% on the pain VAS (28) at 6 month follow-up.

3.3 Secondary Study Endpoints

1. Reduction of previously initiated OA medical therapy (e.g. NSAIDs) at 6 months follow-up.

3.4 Primary Safety Endpoints

1. GAE without major complication.

4.0 Subject Selection and Withdrawal

4.1 General Characteristics of the Proposed Subject Population

Study subjects will be men and women with knee osteoarthritis resulting in knee pain that is refractory to conservative therapies, who are not planning to undergo surgery within 6 months.

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 (20) subjects will be enrolled between both sites and all are anticipated to complete the study.

4.3 Inclusion Criteria

1. Moderate to severe knee pain (VAS > 50 mm), and
2. Pain refractory to at least 3 months* of conservative therapies (anti-inflammatory drugs, or physical therapy, or muscle strengthening, or intra-articular injections), and
3. Kellgren-Lawrence grade 1, 2 or 3 on radiograph of the knee.
4. Age > 40 years.

*3 months was chosen because this time interval is thought adequate for knee pain to be considered refractory to conservative care.

4.4 Exclusion Criteria

1. Current local infection, or
2. Life expectancy less than 6 months, or

3. Known advanced atherosclerosis, which is known lower extremity vascular or lower extremity symptoms thought to be secondary to arterial vascular disease (eg claudication, ischemic rest pain), or
4. Rheumatoid or infectious arthritis, or
5. Prior knee surgery, or
6. Uncorrectable coagulopathy including INR > 2.5 or platelets < 30,000, or
7. Iodine allergy resulting in anaphylaxis, or
8. Renal dysfunction as defined by GFR (eGFR) of <45 obtained within the past 60 days, or
9. Contraindication for MR Imaging (such as claustrophobia, metallic fragment or foreign bones, implants or prosthesis), or
10. IV contrast allergy characterized by anaphylaxis or anaphylactoid reactions.

4.5 Subject Recruitment and Screening

Subjects will be recruited from orthopedic and interventional radiology clinics at University of North Carolina Healthcare System and the Vascular Institute of Virginia.

4.6 Early Withdrawal of Subjects

4.6.1 Criteria for Removal from Study

1. Subjects will be withdrawn from the study if
    a. a major complication occurs that prevents completion of GAE or the ability to complete the follow up visits, or
    b. at any point at their discretion.

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 GAE.

5.0 Study Treatment or Diagnostic Product Procedures

5.1 Description

Subjects will not initiate any new pain therapy or escalate current therapy for 1 month prior to GAE. They will be given an intravenous dose of antibiotics on the day of the procedure and continue with oral antibiotics for seven days after the procedure. The subjects will be given the choice of receiving intravenous anxiolytic and analgesic medication during procedure or proceeding with local anesthetic only.

Arterial access site will be prepped and draped using sterile technique. Ultrasound-guided access may be used and arterial access will be obtained. An intra-arterial sheath will be placed. Through this sheath a guiding catheter will be used to perform lower extremity angiography on the targeted side either manually or robotically. Using the guiding catheter and a microcatheter, the geniculate arteries supplying hypervascular synovial tissue in the region of the knee joint will be catheterized. If there is uncertainty about the angiographic findings, pre-embolization simulation can be performed with contrasted cone beam CT on the procedure table. This will allow

the operators to know exactly what tissues will be receiving the microspheres. Embozene Microspheres ranging from 40-500 microns*, selected at the operator's discretion based upon size of target vessels, will then be injected under fluoroscopic guidance to prevent reflux and non-target embolization. Injection will continue until an end point of at least 'near stasis' (slowed antegrade flow of contrast). Multiple geniculate arteries may be embolized until neovascularity is no longer seen. A repeat lower extremity angiogram will then be performed to evaluate for success of embolization and to exclude complication. The catheter and sheath will then be removed and hemostasis will be achieved with manual compression or a vascular closure device. The subject subsequently will be discharged home the same day (<23 hours) unless a complication arises that requires inpatient admission for management of the complication. Subjects may be discharged on pain medications as needed for post-operative care (<14 days).

The range in size of particles will allow the operators to discern the safest, most effective size for the vessels targeted. For example, if the catheter can be advanced all the way in to the branch supplying only the synovium, smaller particles can be safely used to induce ischemia in the target tissue. If the catheter cannot be advanced due to tortuous or small caliber vessels, a larger sized particle may be selected. This will allow for proximal embolization without distal penetration into the cutaneous branches, thereby allowing continued blood flow to the skin through collateral pathways (Fig 1-2**). This concept is utilized routinely within embolization procedures are commonly performed.*

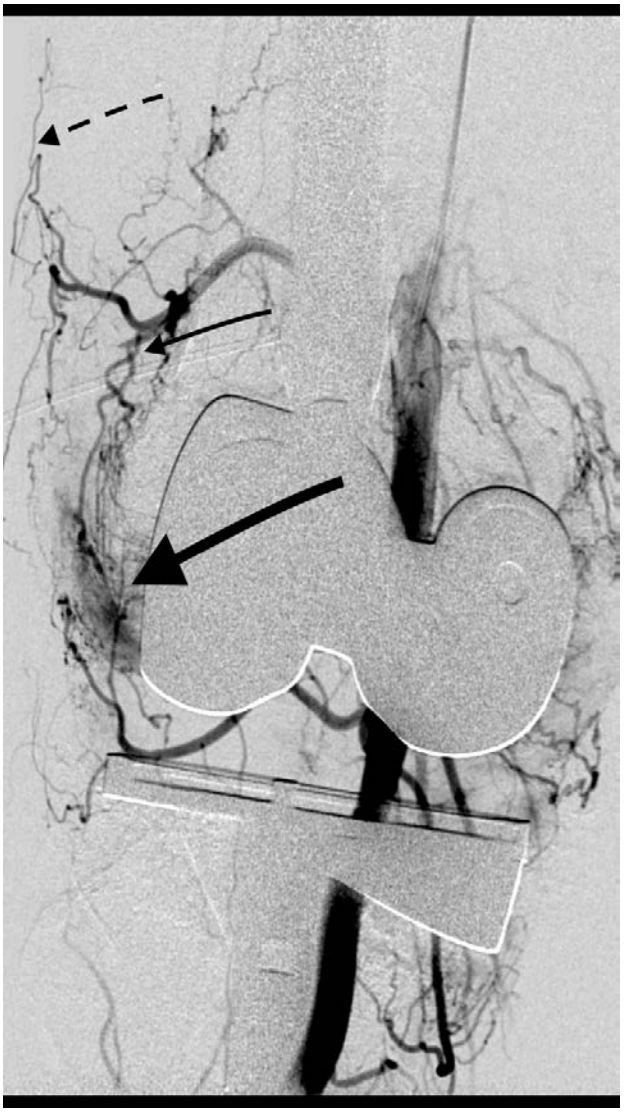

Fig 1.-Geniculate artery angiogram after total knee arthroplasty demonstrating "contrast blush" denoting hypervascular synovium (bold arrow). Separate arterial branches are seen supplying the joint tissue (arrow) and skin (dotted arrow). At this point an attempt would be made to place a microcatheter in the synovial branch. If impossible due to the size of the target vessel, embolization would be performed from this catheter location using larger particles to preserve distal collateral supply to the skin.

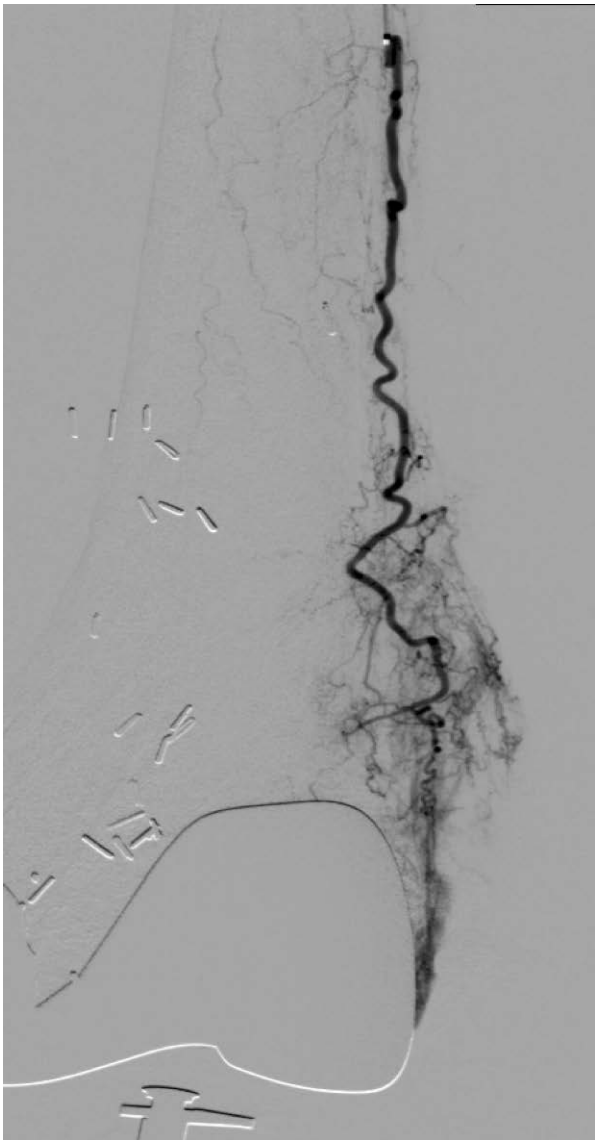

Fig 2. Lateral angiogram of the knee with selective catheterization of the synovial branch of the geniculate artery. In this circumstance, smaller sized embolic particles would be appropriate because cutaneous branches are not seen. This could also be verified with cone beam CT prior to embolization.

It is anticipated that less than 20 milliliters of Embozene will be required for embolization. Embozene Microspheres currently have FDA approval for embolization of hypervascular tumors and arteriovenous 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 (GAE).

5.3 Subject Compliance Monitoring

Study coordinators and physicians will inquire of the subjects to confirm that they have not initiated any new conservative therapies during the follow-up period.

5.4 Prior and Concomitant Therapy

The subjects will be required to have been on conservative therapy for OA for at least three months prior to undergoing GAE. They will be allowed to continue previously initiated therapies throughout the study period, but no new or escalated therapies will be permitted, except post-operative medications (<14 days).

5.5 Blinding of Study

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

5.6 Receiving, Storage, Dispensing and Return

5.6.1 Receipt of Investigational Device Supplies

Embozene Microspheres will be stored within the Interventional Radiology procedural suites. Embolic devices will be labeled 'for investigational use only' and will be reserved for use in the clinical trial.

5.6.2 Storage

Embozene Microspheres must be stored in a cool, dark, dry place in their original packing.

5.6.3 Dispensing

No study specific dispensing techniques will be used.

5.6.4 Return or Destruction of Investigational Device

Embozene Microspheres can be used for other FDA approved indications and will not be destroyed or returned at the completion of the study. Disposable syringes which spherical particulate is stored in will be discarded as medical waste and packaging will be kept in a secure location until the study is completed. Packages will be disposed of upon completion of the study.

6.0 Study Procedures

6.1 Visit 1

Potential enrollees will first be identified and will undergo a standard knee OA work-up to include history and physical exam with emphasis on specific site of knee tenderness. The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire will be administered to assess difficulty as a result of pain, stiffness and overall decreased function secondary to knee pain in the past week. Current pain will also be assessed using a visual analog scale (VAS). A knee radiograph will be obtained and evaluated using the Kellgren-Lawrence grading scale. A baseline knee MRI will also be acquired to evaluate for concomitant pathology as part of routine orthopedic evaluation. For patients that have had an MRI of the knee within the past 90 days, the previous knee MRI will be used as the baseline MRI and new imaging will not be obtained.

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 local study coordinator, co-principal investigator or designee will provide the candidate with a copy of the approved

informed consent and introduction letter for the candidates' review. Written informed consent will be obtained if appropriate. If the patient wishes to take more time to review the study before enrolling, he/she may complete the consent process at the beginning of the next visit, prior to the study GAE procedure. Those candidates who are disqualified from study entry will be logged into the Screening Log with a reason for no study entry. A copy of the consent will be provided to the subject and the original filed in the study files.

6.2 Visit 2 GAE

GAE will be performed as described in part 5.1 above within 4 weeks of Visit 1. Subjects will be given a pager number to reach a physician 24 hours a day to report any adverse symptoms and receive medical advice.

6.3 Visit 3 -1 Day Follow-up

Subjects will be seen in clinic or contacted by phone or by teleconference per the subject's preference the day following GAE (+3 days). As most complications of the procedure will be evident within this time period, this visit is to evaluate for early AE's. If AE is suspected based on change in pain scores or functionality, an MRI will be obtained for further evaluation.

6.4 Visit 4 - 1 Month Follow-Up

Subjects will be seen in clinic 30 +/- 7 days following GAE. The WOMAC questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. An MRI of the treated knee will be acquired.* Subjects will also provide an update about the necessity/frequency of pre-established conservative therapies.

**MRI is only scheduled at one month in order to evaluate for non-target ischemic injury. These types of injuries will become apparent as early as 24 hours after embolization. Infarcted tissue will still be detectable at one month. Based on our experience with embolization in other areas, it is thought extremely unlikely that new ischemic injury related to the procedure will develop after the one-month follow-up. Additionally, findings that would be detected on later scans may be unrelated to the procedure and confound the data.*

6.5 Visit 5 - 3 Month Follow-Up

Subjects will be seen in clinic or contacted by phone or by teleconference per the subject's preference 90 +/- 10 days following GAE. The WOMAC questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. Subjects will also provide an update about the necessity/frequency of pre-established conservative therapies. If AE is suspected based on change in pain scores or functionality, an MRI will be obtained for further evaluation.

6.6 Visit 6 - 6 Month Follow-Up

Subjects will be seen in clinic or contacted by phone or by teleconference per the subject's preference 180 +/- 10 days following GAE. The WOMAC questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. Subjects will also provide an update about the necessity/frequency of

pre-established conservative therapies. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed which may include MRI.

6.7 Study Procedure Flow Chart

7.0 Safety and Effectiveness Assessments

7.1 Safety Assessments

Subjects will be observed for several hours after GAE to monitor for immediate complications to include bleeding, infection and acute ischemia of the lower extremity. The subjects will be given a phone number that they can call to reach the principal investigator or designee if they believe they have developed a complication of the procedure.

7.2 Effectiveness Assessments

Technical success will be defined as devascularization of hypervascular synovium at the affected knee. This will be determined during the procedure. Clinical success will be defined as a 16% reduction of the baseline global WOMAC score at 6 month follow-up (primary outcome) and a 15% reduction of the baseline pain VAS score at 6 month follow-up (secondary outcome).

8.0 Statistical Plan

8.1 Sample Size Determination

Only one small study has examined the use of transcatheter arterial embolization for the treatment of knee pain secondary to OA (12). In that study, the baseline WOMAC total score (mean±SD) was 48.5±9.4. The primary outcome of this study is a 16% reduction in the baseline WOMAC total score. Using the baseline total score from that study, a sample size of 15 will have 80% power to detect a 16% difference (7.8 points) in means, assuming a standard deviation of 10 points. Conservatively, to protect against a potential lost-to-follow-up of 30%, 20 total subjects will be enrolled. This sample size also will ensure adequate power for the secondary outcome, a reduction in the VAS by 15% at 6 months follow-up.

8.2 Statistical Methods

This is a pre-post analytical design and the primary statistical method will be a paired t-test, examining changes from baseline to 6 months. We will use a paired t-test to statistically measure changes resulting from the GAE procedure. Frequencies, including pre-post change, will be reported as percents with 95% confidence intervals. Continuous data will be reported as means with 95% confidence intervals. $P \leq 0.05$ will be considered to indicate statistical significance. All analyses will be performed using SAS software and confidence intervals will be reported as appropriate, including estimates for the appropriate sample size for a larger future study (v9.2, SAS Institute Inc., Cary, NC).

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. The causes of all missing values will be documented with the study data.

8.3 Subject Population(s) for Analysis

A patient will be considered an evaluable study subject evaluable for data analysis per the following criteria, a written informed consent was obtained, he/she meets the inclusion and exclusion criteria, and received the GAE study procedure. All subjects with 6 month follow-up data will be included for analysis even if some 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

An interim analysis will not be conducted.

9.0 Risk Analysis

9.1 Anticipated Risks

Previous studies of lower extremity geniculate artery embolization for arthritis related pain have reported only one complication of moderate puncture site related hematoma (1/13), however this was a small population (12). A recent study of GAE for recurrent hemarthrosis completed by one of the co-PIs (Bagla) included 2/13 subjects who developed transient cutaneous ischemia that resolved within three weeks without intervention (8). Additional risks that are anticipated but occur infrequently after any arterial intervention include infection, pain, pseudoaneurysm formation, arterial dissection and distal non-target embolization resulting in ischemia or necrosis. Detailed risk analysis is below:

	Risk or Side Effect	**Source of Risk or Side Effect**	**Possible**	**Less Possible**	**Rare Event**
Potential Risks Associated Study Enrollment & Study Procedures	Discomfort	Blood draw for lab test, ultrasound or MRI	X		
	Thrombophlebitis, bruising, bleeding, blood clot, Pre-syncope or Syncope (i.e. Fainting)	Blood draw for lab tests		X	
	Anxiety or Claustrophobia	MRI scan		X	
	Psychological Discomfort	Clinical Trial Enrollment			X
	Infection	Blood draw for lab tests			X
	Allergic Reaction	MRI contrast injection			X
	Gadolinium contrast adverse reaction (ie. Nephrogenic Systemic Fibrosis or severe skin reaction from contrast agent only reported in patients with kidney dysfunction)	MRI Contrast injection			X
	Confidentiality breach from Medical Records	Medical Record Keeping			X
	Groin/Anesthetic Injection/Neurologic Injury/ Discomfort/Pain	Pressure during arterial access and after catheter removed at the leg/femoral artery site	X		
	Radiation Exposure Injury	GAE procedure			X
	Kidney Dysfunction	Contrast injected during procedure		X	

Risks of the GAE Procedure and Postoperative care	Joint Infection	GAE Procedure		X	
	Adverse or Allergic Reaction	Intravenous contrast agent or medications administered as part of procedure or follow-up care (ie. MRI contrast)		X	
	Tissue damage to Skin, Muscle, Skin or other structure in legs (Non-target Embolization)	GAE procedure			X
	Minor Bruising or Bleeding	GAE procedure			X
	Bleeding requiring Transfusion or surgery	GAE procedure			X
	Synovitis related symptoms including pain, stiffness or limited joint mobility	GAE procedure	X		
	Post Embolization Syndrome, including fever, malaise, headache, and myalgia (body aches)	GAE procedure		X	
	Internal bleeding, such as Gastrointestinal bleeding	Medications taken after the procedure (ie. Ibuprofen)			X
	Infection	Catheter site in the leg/groin			X
	Arterial injury/trauma, laceration, bruising/pseudoaneurysm	Procedure/ Closure device (clip) on the artery			X
	Pulmonary embolism (clot in lung), Thrombophlebitis (clot in artery or vein)	GAE procedure and immobility			X
	Myocardial Infarction (Heart attack)	GAE procedure including moderate sedation/sedative medication			X
	Stroke	GAE procedure including moderate sedation/sedative medication			X
	Disability	GAE procedure including moderate sedation/sedative medication			X
	Death	GAE procedure including moderate sedation/sedative medication			X

9.2 Risk Minimization

The GAE procedure will be performed by board-certified interventional radiologists who have expertise in endovascular techniques, particularly in selective catheterization and transcatheter embolization techniques. Analgesia during the procedures will be provided through the use of conscious sedation if required. The risks of conscious sedation will be minimized by continuous monitoring of heart rate, blood pressure, oxygen saturation, and

cardiac rhythm. The dose area product projected for the procedure is thought to be less than 30 gray/cm2 which is about 2-4 years of background radiation and significantly less than that of a cardiac catheterization. Radiation exposure will be minimized to subjects under the principal of 'as low as reasonably achievable' (ALARA).

Sterile instruments with a sterile technique will be used to minimize infection risk at the arterial access site. Pre-operative antibiotic(s) will be administered to reduce risk of other infections, such as urinary tract. The arterial access site discomfort will be minimized by administration of local anesthesia into the overlying skin and adjacent tissues. Catheter access into the appropriate artery may be performed using ultrasound-guided arterial puncture to prevent inadvertent vessel puncture with subsequent bleeding. Real-time fluoroscopic monitoring of all catheter/wire manipulations will be used to prevent vascular injury.

Cone beam CT, which provides cross sectional anatomic detail prior to embolization, will be available to the operating interventional radiologist. This angiographic technique can mitigate the risk of non-target embolization. The intent of this technique, as well as meticulous angiographic technique will be used to minimize the risk of non-targeted embolization, that could lead to skin or soft tissue/muscle injury.

The subject will be monitored for the risk of an allergic response to iodinated contrast. To minimize the risk of renal dysfunction there will be use of non-ionic contrast agents, and appropriate pre-procedure hydration, when necessary. Subjects who report an allergic reaction to iodinated contrast will be pre-medicated as per routine allergy prophylaxis per standard of care.

9.3 **Adverse Event Definitions**

Adverse effect. Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s). There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

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

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

- *Hospitalization* shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s) or elsewhere in the current IDE application, as amended.

Unanticipated adverse device effect. 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), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.2 Recording of Adverse Events

Research subjects will be questioned about adverse effects in person or 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 causal 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.

9.3 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.

9.4 Reporting of Adverse Effects and Unanticipated Problems

9.4.1 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.

9.4.2 Reporting Adverse Events to the Responsible IRB

In accordance with applicable policies of the University of North Carolina and Inova Health System 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.

9.5 Stopping Rules

The study will be stopped if there is greater than one major complication (Grade D,E or F) as defined by the Society of Interventional Radiology Classification System for Complications by Outcome (29).

9.6 Medical Monitoring

9.6.1 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 co-PIs, 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 co-PIs. 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 co-PIs.

9.6.2 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.

10.1 Data Handling and Record Keeping

10.2 Confidentiality

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.

10.3 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments involved in the clinical trial.

10.4 Case Report Forms

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.

The coordinator at each site will complete the first CRF together with one of the Co-PIs to verify that it is completed correctly. The coordinator at each site will then be responsible for completing the CRF moving forward. 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 investigators' 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 co-principal investigators 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 either an orthopedic clinic or in an interventional radiology clinic within the UNC Healthcare systems or Vascular Institute of Virginia. The procedures will be performed in UNC Interventional Radiology or Vascular Institute of Virginia. procedural suites. Follow-up visits will occur at UNC IR clinics, or Vascular Institute of Virginia, or via phone or teleconference.

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. Alternate training modules, as requested by local IRB, may also suffice.

Drs. Bagla and Isaacson (fellowship trained interventional radiologists with subspecialty board certification) will be the only primary operators for each of the GAE's. Dr. Bagla has performed more than 600 arterial embolization procedures. Dr Isaacson has performed approximately 250 arterial embolization procedures.

Any of the investigators may conduct follow-up visits as determined by the subjects' and investigators' availability.

All subjects will be coded by an alphanumeric identifier (letters [initials] and site number) and subject identity will be kept confidential. Subjects will be apprised during the informed consent review that they have the right to

voluntarily withdraw from the study at any time for any reason, and that his decision will not affect his medical care, but for attrition analysis subjects will be asked their reason for withdrawal .

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 safety monitor of all Unanticipated Problems/SAE's.

The research coordinator and co-principal investigators 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 is an investigator on the research.

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 safety monitoring after treatment is complete for subject 1, 5, 10, and 20. 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. Data will be maintained in a secure location for the appropriate duration as described in section 10.4. At the conclusion of this term, all paper forms will be shredded and destroyed. 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

Grant from Boston Scientific Corporation.

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 will not be remunerated for study participation.

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 Appendices

1. Study Device (Embozene Microspheres)

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