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NYU Langone Health

Prospective Pilot Study on Geniculate Artery Embolization for Treatment of Persistent Knee Pain Post Total Knee Arthroplasty

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Protocol Signature Page

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations.

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Food and Drug Administration (FDA) and Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations (if applicable), and ICH E6(R2) GCP guidelines.

_____ _____

Signature of Principal Investigator Date

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Table of Contents

List of Abbreviations

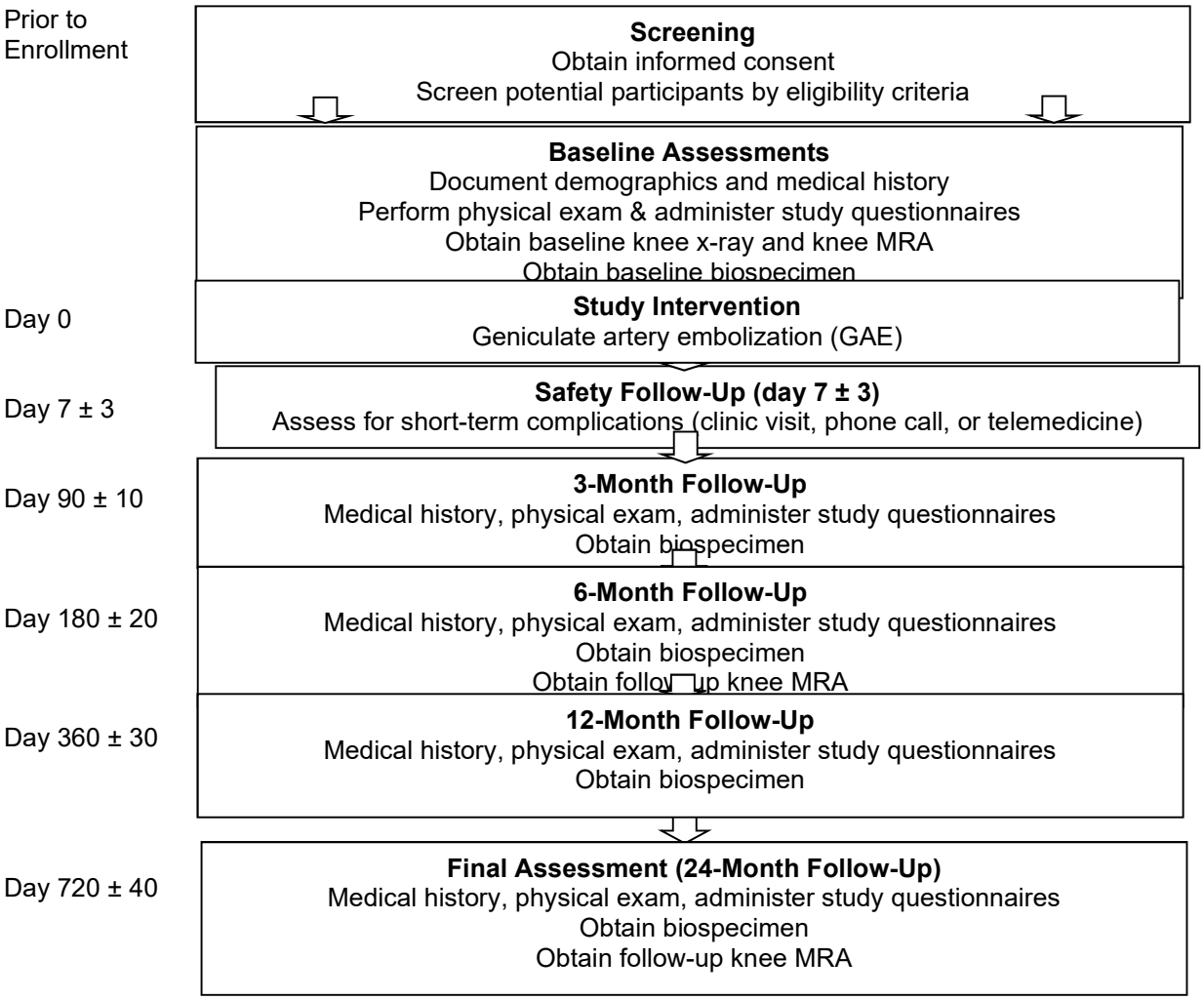
AE	Adverse Event/Adverse Experience
ALARA	As Low As Reasonably Achievable
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GAE	Genicular Artery Embolization
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
KOOS	Knee Injury and Osteoarthritis Outcome Score
MRA	Magnetic Resonance Angiogram
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OA	Osteoarthritis
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
TKA	Total Knee Arthroplasty
US	United States
VAS	Visual Analogue Scale

Protocol Summary

Title	Prospective pilot study on geniculate artery embolization for treatment of persistent knee pain post total knee arthroplasty
Short Title	Geniculate artery embolization for post TKA pain
Brief Summary	Single-arm, single-center, no sham or placebo, prospective pilot trial designed to evaluate the safety and efficacy of transcatheter arterial embolization in patients with persistent knee pain resistant to conservative management for at least **9 months** after total knee arthroplasty (TKA). Eligible participants will receive geniculate artery embolization (GAE) using Embozene™ Color-Advanced Microspheres. Patients will be followed up for a total of 24 months after GAE.
Phase	Pilot study
Objectives	**Primary objective:** to determine the effectiveness of GAE in reducing knee pain at 6-months post GAE in patients with persistent knee pain after TKA. This will be assessed by evaluating the clinical success rate defined as at least 15% improvement in Knee injury and Osteoarthritis Outcome Score (KOOS) pain score from baseline to follow-up visit at 6 months post-intervention without an increase in baseline incidence of pain medication use or intra-articular injections. **Secondary objectives:** - To evaluate the safety of GAE - To determine feasibility and technical success of GAE - To determine whether GAE improves knee symptoms and quality of life (QOL) - To determine the effect of GAE on disease-specific biomarkers in the blood, urine, and synovial fluid of the target knee
Methodology	Prospective, single-arm (no sham or placebo), single-center
Endpoint	**Primary Efficacy endpoint:** KOOS pain score at 6-months post intervention **Secondary endpoints:** - Rate, type, causality, and severity of adverse events (AEs) - KOOS scores at 3-, 6-, 12-, and 24-month visits - QOL index value at 3-, 6-, 12-, and 24-month visits - Pain visual analog scale (VAS) at 3-, 6-, 12-, and 24-month visits - Magnetic Resonance Angiogram (MRA) findings at 6 and 24-month visits
Study Duration	4 years
Participant Duration	Each individual subject will be enrolled for approximately 25 months to complete all study visits from the initial screening visit to last follow up at 24-months post intervention
Population	40 patients, age 30-85, of any gender, with knee pain resistant to conservative management for at least 9 months post TKA.
Study Sites	NYU Langone Health Hospitals
Number of participants	Data from 40 patients who complete 6-month visit will be required The study would enroll 50 patients to account for an attrition rate of 20%
Description of Study Agent/Procedure	Embozene™ Color-Advanced Microspheres are spherical, tightly calibrated, biocompatible, non-resorbable, hydrogel microspheres coated with an inorganic perfluorinated polymer used for embolization.
Key Procedures	GAE; a transcatheter arterial embolization of one or more genicular artery(ies) using Embozene™ Color-Advanced Microspheres

Statistical Analysis	The primary objective is to assess the clinical success rate, which will be summarized in terms of the observed proportion of patients manifesting a positive response and a two-sided exact 95% confidence interval (CI) per the Blyth-Still-Casella method. The treatment will be declared a success if the data support the conclusion that at least 75% of treated patients show a positive response. Preliminary analysis will be performed after 25% (10 subjects) of study sample size complete the 6-month follow-up visit.

Schematic of Study Design



1 Introduction, Background Information and Scientific Rationale

1.1 Background Information and Relevant Literature

Knee osteoarthritis (OA) is common and major cause of pain and disability, that affects approximately 12% of Americans aged 60 and above [1]. Its prevalence is rising due to an aging population and the high prevalence of obesity [2]. Radiographically confirmed symptomatic knee OA affects approximately 3.8% of people worldwide, and knee and hip OA ranked as the 11th highest contributor to global disability [3]. Disabling symptoms of knee osteoarthritis are seen in an approximately 10 % of people over 55 years old [4]. Studies have shown that the cost for health services among persons with OA exceeded those without OA by 1.5- to 2.6-fold [1, 5-9]. The first national, population-based study of health care utilization in persons with knee OA shows that knee OA cohort had on average 6.0 more annual MD visits (95% confidence interval [CI]: 4.7, 7.4) and 3.8 more non-MD visits (95% CI: 2.8, 4.7) than the OA-free cohort [1]. This study used the 2003 Medicare Current Beneficiary Survey, a population-based survey of Medicare beneficiaries linked to Medicare claims, we selected a national cohort of community-dwelling persons aged 65 and older with knee OA. Therefore, the prevalence and burden of knee OA presents a major challenge for health systems globally [3].

Knee OA is a complex, multifactorial disease with no known cure. Risk factors for knee OA include joint injury, bone and joint shape, muscle strength and mass, obesity, gender, metabolic factors, nutrition and vitamin factors, bone density, psychological health and occupation [10, 11]. Treatment seeks to manage symptoms, but adequate symptom control can be difficult to achieve [10-12]. Evidence-based treatment options for knee OA include intra-articular corticosteroids, exercise, education, weight management, and oral medications such as acetaminophen and non-steroidal anti-inflammatories for minor symptoms [13]. Total knee arthroplasty (TKA) is reserved for those with severe joint disease, pain and functional limitations, and is an effective intervention for treatment of chronic knee pain and disability in patients with knee OA [14-16]. However, approximately **10% to 44%** of patients experience **persistent chronic pain after TKA** [17, 18], with the highest-quality studies reporting an incidence of approximately 20% [17]. Persistent postsurgical pain is defined as persistent pain of at least three to six months duration that develops or increases in intensity after surgery and affects health-related quality of life [19, 20]. After TKA, patients with persistent pain may be disappointed with the outcome as pain severity plateaus [21-23]. In addition, the economic impact of long-term, moderate-to-severe, and unexplained pain after TKA is profound, particularly in aging population [24].

An in-depth understanding of OA pathophysiology is emerging [2]. Recently, angiogenesis has been implicated in OA by contributing to structural damage, inflammation and pain [25]. Angiogenesis is blood vessel overgrowth from pre-existing vasculature and is essential for growth, development and tissue repair [25]. However, in OA, angiogenesis increases in articular cartilage, synovium, meniscus, and osteophytes, and at the osteochondral junction [26-30]. Because angiogenesis is accompanied by sensory nerve growth, perivascular nerve growth into normally aneural structures such as articular cartilage and meniscus is thought to contribute to OA pain through chemical and mechanical stimulation of newly formed nerves. Modifying angiogenesis and associated nerve growth is a potential treatment pathway to affect the pathogenesis and symptoms of OA [25]. Angiogenesis inhibitor treatment decreased pain-related behavior in animal models [26]. The mechanism of symptomatic relief is unclear but could include reduced synovitis, reduced periarticular innervation and nociception, and maintaining the integrity of the osteochondral junction [25, 26].

While the etiology of persistent pain following TKA is multifactorial [31], there is growing evidence that synovitis and patient-specific inflammatory response to surgery may influence the long-term clinical outcome following TKA [32, 33]. Murakami et al reported that 80% of patients with persistent knee pain following TKA had moderate to severe synovitis compared to only 19% of patients without persistent pain ($p<0.001$) [34]. In a study performed on 46 patients by Kurien T. et al, patients with moderate-to-severe postoperative pain demonstrated higher grades of Hoffa synovitis ($P<0.001$) and knee effusion volume ($P<0.001$) [33]. In OA patients, the extent of synovitis is associated with increased angiogenesis [35]. Nerve growth is linked to angiogenesis in the osteoarthritic joint and has been theorized to be as a potential source of pain in OA patients [25]. Given that removal of the synovium is left to surgeon preference [36], we theorize that unaddressed neovascularity and neural growth may be contributing to persistent post TKA pain.

Over the past decade, GAE has been evaluated for the treatment of knee OA, showing significant improvement in knee pain, function, and quality of life [12, 37-40]. In a study by Okuno et al, The Whole-Organ Magnetic Resonance Imaging Score (WORMS) was evaluated at baseline and at 2 years after embolization in 35 knees and showed

significant improvement of synovitis vs baseline (P < .0016) and no osteonecrosis or other evidence indicating aggressive progression of degenerative changes [37]. In an animal study, it's been shown that GAE can limit inflammation in the synovium of OA-affected knees [41]. In a recent abstract accepted as oral presentation during the society of interventional radiology 2023 annual meeting, investigators assessed the efficacy of GAE in this patient population. The preliminary results suggest that GAE in post-TKA patients may be a promising intervention to treat persistent symptoms in this previously challenging patient population [42]. The corresponding study was published in the Journal of Vascular and Interventional Radiology by Taslakian et al. The study reported a clinical success rate of 83% of patients with knee OA post GAE [43].

The goal of this proposed prospective, single-center, single-arm trial is to evaluate the safety and efficacy of GAE for treatment of persistent postsurgical knee pain following TKA.

1.2 Name and Description of the Investigational Agent

The investigation agent (device) in this trial is Embozene™ Color-Advanced Microspheres.

Embozene™ Color-Advanced Microspheres are spherical, tightly calibrated, biocompatible, nonresorbable, hydrogel microspheres coated with an inorganic perfluorinated polymer (Polyzene™-F). The microspheres intended to occlude vasculature for the purpose of blocking blood flow to a target tissue. They are available in prefilled syringes in a range of sizes suitable for embolic therapy. The microspheres are compressible to enable smooth delivery through the indicated delivery catheter and color-coded by size to allow for easy identification. In this trial, we intend to use **100 µm microspheres**.

Embozene™ Color-Advanced Microspheres are supplied in a 20 ml syringe prefilled with 2 ml of product suspended in a non-pyrogenic, sterile transport solution of physiological saline. The total volume of Embozene™ Color-Advanced Microspheres including transport solution is approximately 7 ml. Prefilled syringes of Embozene™ Color-Advanced Microspheres are packaged in a sterile, sealed tray with a peel-away lid. The label indicates the specific size of the microspheres contained in the syringe.

Embozene™ Color-Advanced Microspheres are intended for embolization of arteriovenous malformations and hypervascular tumors, including uterine fibroids and hepatoma, and for embolization of prostatic arteries for symptomatic benign prostatic hyperplasia. This device is not intended for neurovascular use. The device is FDA approved for above indications (FDA approved for treatment of benign prostatic hyperplasia; FDA 510(K) # K180102; 510(k) premarket notification of intent to market the device FDA 510(k) # K141209)

There are no known chemical interactions between Embozene™ Color-Advanced Microspheres and pharmaceuticals.

Additionally, for labeling with Magnetic Resonance (MR) compatibility, the proposed Embozene™ Color-Advanced Microspheres were assessed and met requirements in the Guidance for Industry and Food and Drug Administration Staff Establishing Safety and Compatibility of Passive Implants in the MR Environment. Embozene™ Color-Advanced Microspheres are labeled MR safe in the device Direction for Use (DFU) [**Attachment 1**].

U.S. FDA has granted the company Breakthrough Device Designation for its Embozene® microspheres for genicular artery embolization (GAE) for symptomatic knee osteoarthritis. Embozene is a medical device that is FDA cleared for the embolization of hypervascular tumors, arteriovenous malformations, uterine fibroids and benign prostatic hyperplasia.

Device DFU is attached to this protocol [Attachments 1]

An Investigational Device Exempt (IDE) was obtained from the FDA (IDE approval # G230245). IDE approval letter dated October 6, 2023 is attached to this protocol submission [attachment 2].

1.2.1 Preclinical Data

Non-clinical tests performed on the Embozene Microspheres, reference device, provide reasonable assurance that the proposed device has been designed and tested to assure conformance to the requirements for its intended use. As the device received FDA approval for additional indications lately (prostate artery embolization), we believe that

using the device for GAE in this trial (for treatment of knee pain) does not require additional bench, biocompatibility, sterilization, or pre-clinical animal testing beyond what was required for the reference device. All existing testing provided in the previous Embozene Microspheres premarket submissions remains applicable.

Biocompatibility testing provided in the previous Embozene Microspheres premarket notification included: cytotoxicity, sensitization, irritation, sub-acute and sub-chronic systemic toxicity, systemic toxicity- material mediated pyrogenicity, genotoxicity (bacterial mutagenicity, in-vitro chromosome aberration, in-vivo micronucleous assay), implantation, hemocompatibility (hemolysis, partial thromboplastin time, platelet/leukocyte counts). All tests passed, indicating that the device materials are biocompatible for its intended use.

Performance testing provided in the previous Embozene Microspheres premarket notification included: microsphere size distribution, visual inspection, Ph of transport solution, osmolality of transport solution, microsphere suspension, catheter compatibility, and elution test. all tests passed demonstrating the device meets the predetermined performance requirements.

Published literature on preclinical animal studies assessed the biocompatibility, safety, and efficacy of Embozene Microspheres in comparison with the Embosphere predicate and other embolization devices. The devices were evaluated in a porcine kidney model to determine arterial distribution characteristics, inflammation and recanalization, impact on inflammatory tissue and foreign body reaction, and immunohistochemical inflammatory reactions. The results demonstrate a similar biological tissue response between the Embozene Microspheres and the Embosphere predicate device which supports substantial equivalence [44].

A study by Stampfl et al, evaluated the inflammatory response and recanalization after embolization with the embolic agent based on a core and shell design with a hydrogel core of polymethylmethacrylate (PMMA) and a Polyzene-F nanoscale coating in a porcine kidney model [45]. It demonstrated good biocompatibility of the embolic material. As in other spherical embolic agents, recanalization can occur to some degree.

Additionally, for labeling with MR compatibility, the proposed Embozene Microspheres were assessed and met requirements in the Guidance for Industry and Food and Drug Administration Staff Establishing Safety and Compatibility of Passive Implants in the MR Environment. The device is labeled as “MR safe” in the DFU [attachment 1]

1.2.2 Clinical Data to Date

Embozene Microspheres have been already investigated in several clinical studies for multiple indications. Stampfl U et al, investigated the safety and efficacy of uterine artery embolization using narrow-size-range polyphosphazene-coated hydrogel microspheres. Results demonstrated that uterine artery embolization with Embozene microspheres is a safe procedure. Its efficacy is demonstrated by high fibroid devascularization and volume reduction rates and significant improvements of clinical symptoms and quality-of-life scores during follow-up [46]. Sneets el al, demonstrated that Polyzene F–coated hydrogel microspheres for uterine artery embolization resulted in good dominant and overall tumor infarction in most patients, with corresponding improvement of symptoms [47].

GAE was also investigated for the treatment of recurrent hemorrhage after hip and knee arthroplasty. Kalmar et al demonstrated 100% technical success rate, no procedure-related complications, and effectiveness in patients without underlying coagulopathy in preventing recurrences of spontaneous recurrent hematoma or hemarthrosis of the hip and the knee [48-50].

Recently, multiple trials demonstrated the safety and efficacy of GAE for treatment of knee pain in patients with knee OA [12, 37-40, 51-53]. Okuno et al, investigated the effects of embolizing abnormal blood vessels in people with mild to moderate knee OA [12]. Fourteen participants received transcatheter arterial embolization of abnormal branches of the genicular artery using imipenem and cilastatin sodium or 75 μm Embozene microsphere. WOMAC pain and function scores improved substantially at 1-, 4-, and 12-months post procedure. No major AEs occurred. One participant had a moderate subcutaneous hemorrhage at the puncture site that resolved within 1 week.

In a follow-up study, Okuno et al, described the safety and efficacy of transcatheter arterial embolization in 72 patients with mild to moderate radiographic knee OA [37]. Clinical outcomes were evaluated at 1, 4, and 6 months

and then every 6 months for a maximum of 4 years. Mean WOMAC pain scores significantly decreased from baseline to 1, 4, 6, 12, and 24 months after treatment (12.1 vs 6.2, 4.4, 3.7, 3.0, and 2.6; all P <.001). The WORMS score was evaluated at baseline and at 2 years after embolization in 35 knees and showed significant improvement of synovitis vs baseline (P < .0016) and no osteonecrosis or other evidence indicating aggressive progression of degenerative changes. There were no major AEs related to the procedures. Specifically, there was no incidence of tissue necrosis, dermal ulcers, or peripheral paresthesia in any embolized territory during the follow-up period. Moderate subcutaneous hemorrhage at the puncture site in 12 patients resolved within 1 week. Four of seven patients treated with Embozene showed transient cutaneous color change on the treated knee, which resolved spontaneously within 1 month.

A study by Bagla et.al, showed improvement in the pain scores in 20 patients with knee osteoarthritis. The mean VAS improved from 76 mm ± 14 at baseline to 29 mm ± 27 at 6-month follow-up (P <.01). The mean WOMAC score improved from 61 ± 12 at baseline to 29 ± 27 at 6-month follow-up (P < .01). Self-limiting skin discoloration occurred in 65% patients and 10% of patients developed transient plantar sensory paresthesia [51].

A study by Padia S et al evaluated the safety and effectiveness of GAE in patients with knee OS (grades 2, 3, 4). Knee OA severity was grade 2 in 18% of the patients, grade 3 in 43%, and grade 4 in 40%. Technical success was achieved in 100% of the subjects. The WOMAC total and VAS pain scores decreased by 61% and 67% at 12 months from a median baseline of 52 (of 96) and 8 (of 10), respectively. Twenty-seven patients (68%) had a reduction of ≥50% in both WOMAC total and VAS pain scores [40]. Multiple meta-analysis of the published data show consistent results, confirming the safety and efficacy of GAE for treatment of knee OA [40, 54-57].

A recent study by Taslakian et al, reported a clinical success rate of 83% of patients with knee OA post GAE [43]. The study also evaluated the role of GAE as a disease modifying treatment option for knee OA by assessing systemic disease-specific biomarkers. The study found decreased neuron growth factor (NGF levels) following GAE which may contribute to pain reduction and slowing of cartilage degeneration.

1.2.3 Dose Rationale
Not applicable.

1.3 Rationale
While the etiology of persistent pain following TKA is multifactorial [31], there is growing evidence that synovitis and patient-specific inflammatory response to surgery may influence the long-term clinical outcome following TKA [32, 33]. Murakami et al reported that 80% of patients with persistent knee pain following TKA had moderate to severe synovitis compared to only 19% of patients without persistent pain (p<0.001) [34]. In a study performed on 46 patients by Kurien T. et al, patients with moderate-to-severe postoperative pain demonstrated higher grades of Hoffa synovitis (P<0.001) and knee effusion volume (P<0.001) [33]. In addition, in OA patients, the extent of synovitis is associated with increased angiogenesis [35]. Nerve growth is linked to angiogenesis in the osteoarthritic joint and has been theorized to be as a potential source of pain in OA patients [25]. Given that removal of the synovium is left to surgeon preference [36], we theorize that unaddressed neovascularity and neural growth may be contributing to persistent post TKA pain. This rational is supported by multiple recent studies of GAE for treatment of knee OA, that showed the safety and efficacy of this treatment option for patients with knee OA [12, 37-40, 51-53]. In addition, the recent study by Taslakian et al, showed statistically significant reduction in the nerve growth factor (NGF) after 12 months post GAE in patients with native knee OA [43].

1.4 Potential Risks & Benefits
1.4.1 Known Potential Risks
Potential AEs related to the use of the device from the device insert of directions for use (DFU) [attachment 1] and recent literature [12, 37-40, 48-53].

- Possible AEs:

- Incomplete occlusion of vascular beds or territories may give rise to the possibility of post-procedural development of alternative vascular pathways, recanalization, or recurrence of symptoms
- Post-embolization syndrome including fever, malaise, headache, and myalgia (body aches)
- Transient, self-resolving cutaneous purpura / skin color change
- Transient plantar or peripheral sensory paresthesia

- Synovitis related symptoms including pain, stiffness or limited joint mobility

- Rare AEs:

- Allergic reaction and foreign body reactions (e.g., pain, rash, fever, inflammation)
- Capillary bed saturation and tissue damage
- Infection
- Neurological deficits
- Thrombosis
- Undesirable reflux, passage/migration or placement of Embozene™ Microspheres, resulting in non-target embolization, ischemia, and / or ischemic infarction.
- Non-target embolization to lower extremity vasculature resulting in vascular thrombosis and limp threatening ischemia
- Vessel or lesion rupture
- Tissue necrosis
- Dermal ulcer
- Tendon or ligament rupture
- Osteonecrosis
- Joint infection
- Syncope due to pain during the study procedures (rare)

- Very rare AEs:

- Death (extremely rare)

Potential AEs associated with angiography and catheterization of vessels:

- Nausea, vomiting, and/or allergic reaction anaphylaxis due to iodinated contrast used during embolization procedure (less possible)
- Contrast-induced renal dysfunction (less possible)
- Access site-related adverse events: bleeding, infection, hematoma formation, arteriovenous fistula, pseudoaneurysm (rare)
- Catheterization-associated adverse events: injury to catheterized vessels including vessel perforation, dissection, vasospasm, or thrombosis (rare)
- Infection (rare)

Potential AEs associated with knee aspiration for biomarker analysis

- Knee infection (rare)
- Bleeding (rare)
- Pain and discomfort

Potential AEs associated with blood draws for biomarker analysis

- Bleeding, bruising
- Pain and discomfort, vasovagal reaction to pain

Potential AEs associated with radiation exposure

- Deterministic radiation risks: Radiation-induced injuries to the skin and underlying tissues, which occur shortly after the exposure (rare)
- Stochastic radiation risks: Radiation-induced malignancy which may occur later in life (rare)

Potential AEs associated with MRA knee (with contrast):

- Discomfort (possible)
- Anxiety or claustrophobia (less possible)
- Peripheral nerve stimulation casing tingling or twitching (rare)
- Injury and burns related to metals (very rare, particularly with the MR screening performed prior to entering MR zone and subjects with contraindications to MR will be excluded from the study)
- Pacemaker dysfunction (very rare; subjects with pacemakers will be excluded from the study)

- Skin burns (very rare)
- Tinnitus and hearing loss (very rare)
- Quench (very rare)
- Pain or discomfort associated with administration of contrast
- Allergic reaction to gadolinium (rare)
- Gadolinium-Associated Nephrogenic Systemic Fibrosis (very rare)

Potential AEs associated with moderate sedation during procedure:

- Over sedation (less possible)
- Nausea, vomiting, and/or allergic reaction to medications / anaphylaxis (rare)
- Respiratory failure, myocardial infarction, and death (rare)

Potential risks associated with study enrollment and ancillary study procedures:

- Discomfort due to blood draws required for the study (possible)
- Minor local discomfort due to the pressure of the ultrasound transducer on the skin during arterial access (possible)
- Inconvenience at having to return for follow-up visits (possible)
- Discomfort, Thrombophlebitis, bruising, bleeding, blood clot, presyncope or syncope (i.e. fainting) due to blood draws required for the study (less possible)
- Psychological discomfort from clinical trial enrollment and completing study questionnaires (less possible)
- Infection from blood draw for lab tests (rare)
- Loss of confidentiality of medical records (rare)

Risk minimization:

The GAE procedure will be performed by fellowship-trained interventional radiologists who have expertise in endovascular techniques, particularly in selective catheterization and transcatheter embolization techniques. All proceduralist have specific experience in performing the procedure in this study, namely GAE. Specifically, the PI and study investigators also over 3 years of experience in GAE procedures performed for native knee OA (as a part of an ongoing clinical trial preciously approved by the FDA [IDE # G190316] and NYULH IRB). Study investigators have also relevant experience in diagnosis and management of post TKA hemarthrosis and proceduralists have experience in clinically indicated GAE procedures performed for post TKA hemarhtrosis.

Analgesia during the procedures will be provided using conscious sedation if subject opted to receive conscious sedation. 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 around 30-75 gray/cm2.The effective radiation dose is approximately 0.003 mSv from the x-ray of the knee if needed and a mean of 3.0 to 12 mSv from angiography of the lower extremity which is about 2-4 years of background radiation and significantly less than that of a cardiac catheterization [58]. Radiation exposure will be minimized to subjects under the principal of ‘as low as reasonably achievable’ (ALARA). For example, fluoroscopy will be performed with the lowest acceptable exposure for the shortest time necessary to perform the procedure. Methods to reduce radiation-related adverse events include, but not limited to, tight collimation, use of pulsed fluoroscopy, and judicious image acquisition.

Sterile instruments with a sterile technique will be used to minimize infection risk at the arterial access site. 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.

Subjects will be monitored in the immediate post-procedure period in the recovery area for 2-6 hours, depending on method used to achieve hemostasis. This time for monitoring is sufficient as it is a standard monitoring period for endovascular embolization procedures.

Subjects will also be followed up during the safety visit described above to ensure the risks are minimized, and adverse events, if any, are detected and managed in timely manner.

Specific monitoring plan is listed below:

1. Vascular injury / non-target embolization to lower extremity, bleeding, access site complications will be monitored as follows:
    a. On the day of procedure, interventional radiologist (investigator) performing the procedure will assess access site.
    b. Day 7 safety visit: investigator will assess for symptoms in the target lower extremity (pain, swelling at access site and document findings
    c. Follow up visits: investigator will assess groin access site for hematoma, pseudoaneurysm and assess lower extremity pulses
2. Skin ulceration, cutaneous purpura, plantar or peripheral sensory paresthesia will be monitored as follows:
3. Each follow up visit, an investigator will assess for symptoms and signs in the target lower extremity
4. Other AEs, such as osteonecrosis and acute infections will be monitored as follows: each follow up visit, an investigator will assess for symptoms and signs.

1.4.2 Known Potential Benefits

There is no guarantee of benefit to any subject. Potential benefits to the subjects from participating in the study, based on prior clinical data available in the literature regarding GAE for treatment of knee OA [12, 37-40, 51-53] and post TKA hemarthrosis [48-50] are:

- Knee pain reduction
- Physical function improvement
- Synovitis reduction
- QOL improvement

2 Objectives and Purpose

2.1 Primary Objective

The primary objective of the study is to determine the effectiveness of GAE in reducing knee pain at 6-month post intervention. This will be assessed by evaluating the clinical success rate defined as at least 15% improvement of KOOS pain score from baseline to follow-up visit at 6 months post GAE without an increase in baseline incidence of analgesics [59].

2.2 Secondary Objectives

The secondary objectives of the study are to determine

1. Safety of GAE evaluated by cumulative rates of adverse events (AE), as well as type, causality, and severity of each AE.
2. Feasibility / technical success defined as successful selective catheterization of target genicular artery(ies) and embolization from at least one feeding artery of the knee joint (with the embolization endpoint defined as suppression or reduction in the filling of (blood flow in) abnormal vessels visible on angiography (pruning of the distal abnormal vasculature, with patent genicular artery).
3. Whether GAE is effective in improving:
    a. Knee pain using the visual analog scale (VAS) at 3-, 6-, 12-, and 24-month post GAE
    b. Knee symptoms using KOOS scores at 3-, 6-, 12-, and 24-month post GAE [60]
    c. Self-reported quality of life using EQ-5D-5L scale at 3-, 6-, 12-, and 24-month post GAE [61].
    d. Synovitis on MRA at 6- and 24- months post intervention
4. Effect of GAE on disease-specific biomarkers levels

3 Study Design and Endpoints

3.1 Description of Study Design

This study is a single-center, single arm, no sham or placebo, open label, prospective pilot study designed to evaluate the safety and feasibility of GAE for the treatment of knee OA resistant to conservative management for at least 9 months post TKA. Enrolled patients will receive angiography and embolization of the one or more geniculate arteries in the affected knee using 100 µm Embozene microspheres. If both knees are affected and fit eligibility criteria, the knee with the higher pain score on electronic VAS will be targeted.

The primary objective is to evaluate the effectiveness of GAE in reducing knee pain at 6 months. The primary objective will be evaluated by the clinical success rate. Clinical success is defined as at least 15% improvement in KOOS pain score at 6-month post GAE without increase in baseline use of analgesics. 40 patients will be required for this study to evaluate the primary outcome (complete 6-month visit). The study would accrue 50 patients to account for an attrition rate of 20%.

Change in KOOS pain score and VAS pain will be used as a measure of efficacy (i.e., pain reduction). KOOS questionnaire is a widely used, disease-specific measure. It was developed as an extension of the WOMAC score with the purpose of evaluating short-term and long-term symptoms and function in subjects with knee injury and osteoarthritis [60]. Specifically, the KOOS questionnaire assesses 5 domains: knee pain, knee symptoms/stiffness, knee function (activities of daily living), knee function (sports/recreational activities), and knee related quality of life.

The electronic VAS is a horizontal line with no markings on the scale except “No pain” on the left (score: 0 mm) and “worst possible pain” on the right end of the scale (score: 100 mm). Subjects mark the VAS to indicate their current pain level, with 0 mm representing "No pain" and 100 mm representing "worst possible pain". In our study, subjects will be asked to mark their pain level on a paper VAS on study questionnaire form and will give a score between 0 to 100, which will be documented on the appropriate eCRF.

All study variables will be collected on source documents (paper forms, study questionnaire forms, and/or electronic medical system) at the time of each clinic visit and transferred to eCRFs (TrialMaster) by IRB-approved study coordinator or investigator. The paper source documents will be placed in secure locked folders with other study documents (such as signed consent forms). The remainder of the source documents will be in the electronic medical record system.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoint is the KOOS pain score at 6 months post intervention.

3.2.2 Secondary Study Endpoints

Secondary efficacy endpoints are:

1. KOOS scores at 3-, 6-, 12-, and 24-month post GAE
2. VAS pain at 3-, 6-, 12-, and 24-month post GAE
3. Self-reported quality of life using EQ-5D-5L scale at 3-, 6-, 12-, and 24-month post GAE
4. MRA findings at 6- and 24-month post GAE
5. Pain medication usage at 3-, 6-, 12-, and 24-month post GAE
6. Feasibility / technical success
7. Knee-specific biomarkers at 3-, 6-, 12-, and 24-month post GAE
8. Number/rate, severity, and description of complications, adverse events, or poor outcomes that are secondary to the procedure, which will be summarized using counts and simple statistics (i.e., mean number of patients with complications.)

3.2.3 Exploratory Endpoints

Not applicable.

4 Study Enrollment and Withdrawal

4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all the following criteria:

1. 30-85 years of age, of any gender
2. Knee pain resistant to conservative treatment for at least 9 months* post TKA performed for knee OA
3. Moderate to severe knee pain: pain VAS ≥40 mm
4. Willing, able, and mentally competent to provide informed consent and complete study questionnaires in English. The validated KOOS study questionnaires are only available in English.

* Conservative management is defined for the purpose of this study as use of analgesics (anti- inflammatory drugs, acetaminophen), or physical therapy and muscle strengthening exercises); 9-month duration of pain was selected because this time interval is adequate for knee pain to be considered refractory to conservative care.

Note: If both knees meet criteria, the one with a higher VAS score will be selected for the study (i.e., target knee).

4.2 Exclusion Criteria

An individual who meets **any of the following criteria** will be excluded from participation in this study:

1. Active systemic or local knee# infection
2. Active malignancy
3. Life expectancy less than 6 months
4. Prior ipsilateral knee arthroscopic surgery or repeat TKA (within 9 months of screening)
5. Ipsilateral knee intra-articular injection in the last 3 months
6. Rheumatoid arthritis, spondyloarthropathies, crystal disease, gout, pseudogout, or lupus
7. Pregnant during the study period
8. Renal dysfunction as defined by serum creatinine >1.6 dl/mg or eGFR <60 on blood tests obtained within 30 days of procedure
9. Body weight greater than 200 Kg
10. Known history of severe contrast allergy to iodinated contrast resulting in anaphylaxis
11. Known significant arterial atherosclerosis that would limit selective angiography and/or lower extremity symptoms thought to be secondary to arterial vascular disease (eg claudication, ischemic rest pain)
12. known avascular necrosis in the target knee
13. Complications of TKA such as suspected or confirmed early loosening, ligamentous instability, reflex sympathetic dystrophy, polyethylene wear with or without particle disease (osteolysis), patellofemoral mal-tracking, referred hip and low back pain, and large effusions** (with or without hemarthrosis) on available imaging studies such as knee radiographs, computed tomography scans, and / or the MRA performed for the study purposes.
14. Patient is enrolled in a different trial for treatment of knee pain post total knee arthroplasty (ipsilateral knee)

using Musculoskeletal Infection Society (MSIS) criteria for diagnosis of prosthetic joint infection

2011 Musculoskeletal Infection Society (MSIS) criteria [1]
PJI is present when 1 major criteria exist or 4 out of 6 minor criteria exist
Major criteria: ▪ 2 positive periprosthetic cultures with phenotypically identical organisms ▪ A sinus tract communicating with the joint
Minor criteria: ▪ Elevated CRP and ESR ▪ Elevated synovial fluid WBC count or ++ change on leukocyte esterase test strip ▪ Elevated synovial fluid PMN% ▪ Presence of purulence in the affected joint ▪ Positive histologic analysis of periprosthetic tissue ▪ A single positive culture

* Patients with contraindications to MRA or gadolinium administration such as claustrophobia, metallic fragment/implants, pacemaker, or severe gadolinium associated contrast allergy can be enrolled and MRA will not be performed in these patients.

** if pain persists after aspiration of a large knee effusion, a potential subject can be enrolled.

Note: Absence of exclusion criteria will be confirmed by orthopedic investigator and / or medical record from available orthopedic surgery notes if within one month of enrollment.

4.3 Vulnerable Subjects

The study does not intend to recruit vulnerable subjects. The study will not recruit any children, pregnant women, or prisoners.

4.4 Strategies for Recruitment and Retention

Participants will be recruited at the study investigator or sub-investigator clinical practices, via brochures / social media, and through an EPIC search.

Study Investigator Or Sub-Investigator Clinical Practices

A study investigator or sub-investigator will assess the medical record of potential subjects for eligibility and provide eligible participants with information regarding the study during the initial study visit and, if patients are interested, obtain informed consent.

IRB-approved study coordinator or co-investigator will guide interested people through written informed consent. Recruitment is expected to occur over four years. To achieve the primary objective, data from 40 patients will be required (i.e, completed GAE and at least 6 month visit) and the study would accrue 50 patients to account for an attrition rate of 20%.

Only NYULH individuals who are listed on the IRB-approved protocol will approach patients for consent.

Brochures / Social Media

A study brochure [attachment 3] will also be available in NYULH rheumatology, orthopedics, family medicine, and interventional radiology clinics and will be also disseminated on social media (e.g. Facebook, Twitter, blogging) to advertise for the study after IRB approval. The study brochure will include contact information for interested subjects to contact the study coordinator and/or PI.

DataCore/Epic Information for Recruitment

Potential study subjects will often be identified by the orthopedic sub-investigator. This study will utilize EPIC to identify subjects. IRB-approved study personnel will submit a request to NYULH DataCore via iLab after obtaining IRB approval to general a report. The report will be requested to generate a list of potential subjects with a diagnosis of knee pain post TKA and who meet eligibility criteria from the electronic medical system of NYULH.

The research coordinator(s), PI, and co-investigators will have access to EPIC search results / DataCore report throughout the study active enrollment period. The report request will be submitted twice a month during the course of the study. The list will be filtered to identify patients who meet eligibility criteria listed in this protocol.

The PHIs that will be extracted from the EPIC search will be patient's name, MRN, contact information, and name and contact information of the treating physician (TP). The dataset will be deleted after discontinuation, termination, or completion of the study.

Queries regarding eligible subjects will run during the course of the study until discontinuation, termination, or completion of the study.

Once potential subjects have been identified, a study coordinator or investigator will contact the treating physician (orthopedic surgeon who performed the TKA and following the patient) in person . Once clearance is obtained from treating physician, a study team member will inform the potential subjects about the study using the study brochure [attachment 3] and standard language [attachments 4&5].

Patients may be contacted by email, the MyChart portal, MyChart recruitment tools through DataCore, and/or direct phone call using standard language [attachment 4]. When sending recruitment information by email, SendSafe Secure email will be used to contact patients.

Once contact is made, the IRB-approved study brochure or language included in the approved study brochure (if contact made by phone) will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact the VIR research coordinator or the PI at Bedros.Taslakian@nyulangone.org or at the office number 212-263-5898. The contact information will also be available on the study brochure. If patient agrees to participate, he will be scheduled for a clinic visit with one of the investigators (visit 1) to further discuss the study, complete the screening elements, and obtain informed consent.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact study coordinator or have subjects contact research-contact-optout@nyumc.org or 1-855-777-7858.

4.5 Duration of Study Participation

Each subject will be enrolled in the study for approximately 25 months from the initial screening visit until the last follow-up visit at 24 months post intervention.

4.6 Total Number of Participants and Sites

Data from 40 participant will be required and the study would accrue 50 patients to account for an attrition rate of 20%. Withdrawn subjects and subjects who did not completed at least the 6-month visit can be replaced.

The study will be conducted only at NYULH Hospitals. No subjects will be enrolled at external national or international sites.

4.7 Participant Withdrawal or Termination

4.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any AE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the investigator that continued participation is not in the best interest of the patient;
- Pregnancy during study period;
- At the desertion of the study PI if patient fails to comply with protocol requirements or study-related procedures, including failure to attend any of the study visits within the protocol-defined window;
- Termination of the study by the Sponsor, the regulatory authority, FDA, or IRB.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

4.7.2 Handling of Participant Withdrawals or Termination

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the follow-up visits. The reason for patient withdrawal must be documented. In the case of loss of follow-up, attempts to contact the patient will be made and documented in the patient's medical records. Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs). Withdrawn patients can be replaced (do not count toward the protocol-defined sample size).

4.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the IDE sponsor and regulatory authorities. If the study is

prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

5 Study Agent (Study device) and Procedural Intervention

5.1 Study Agent(s) and Control Description

Embozene™ Microspheres are spherical, tightly calibrated, biocompatible, nonresorbable, hydrogel microspheres coated with an inorganic perfluorinated polymer (Polyzene™-F). The microspheres are intended to occlude vasculature for the purpose of blocking blood flow to a target tissue. They are available in prefilled syringes in a range of sizes suitable for embolic therapy. The microspheres are compressible to enable smooth delivery through the indicated delivery catheter and color-coded by size to allow for easy identification. **100 µm microsphere will be used and are supplied in prefilled syringes**.

Embozene Microspheres are intended for embolization of arteriovenous malformations and hypervascular tumors, including uterine fibroids and hepatoma, and for embolization of prostatic arteries for symptomatic benign prostatic hyperplasia. This device is not intended for neurovascular use. The device is FDA approved for above indications (FDA approved for treatment of BPH; FDA approval 510(K) # K180102; 510(k) premarket notification of intent to market the device FDA 510(k) # K141209)

There are no known chemical interactions between Embozene Microspheres and pharmaceuticals.

IDE for the purpose of this study was obtained from the FDA.

5.1.1 Acquisition

Embozene™ Microspheres will obtained from the manufacturer.

5.1.2 Formulation, Appearance, Packaging, and Labeling

Embozene Microspheres are supplied in a 20 ml syringe prefilled with 2 ml of product suspended in a non-pyrogenic, sterile transport solution of physiological saline. The total volume of Embozene Microspheres including transport solution is approximately 7 ml. Prefilled syringes of Embozene Microspheres are packaged in a sterile, sealed tray with a peel-away lid. The label indicates the specific size of the microspheres contained in the syringe. 100 µm microsphere will be used and are supplied in prefilled syringes.

5.1.3 Product Storage and Stability

As per manufacturer's instructions specified in the DFU, the device should be stored in a cool, dry, dark place. Product must be used prior to expiration date on label. The investigational device will be stored in a secure locked cabinet in the interventional radiology storage area (Tisch hospital, 2nd floor) and only the PI, investigators, and research coordinator will have access to the lock.

5.1.4 Preparation

Embozene Microspheres are supplied in a 20 ml syringe prefilled with 2 ml of product suspended in a non-pyrogenic, sterile transport solution of physiological saline. The total volume of Embozene Microspheres including transport solution is approximately 7 ml.

Prior to embolization, the transport solution will be eliminated from the syringe. An embolic mixture will be prepared by adding 9 cc saline + 9 cc iodinated contrast added to the 2 cc of product (Embozene Microspheres) for a total of 20 cc embolic mixture.

5.1.5 Dosing and Administration
The embolic mixture will be injected in small increments until embolization end-point (pruning of distal vasculature) in the target artery is reached (0.5-1 cc embolic mixture injected over 2 minutes, followed by 1 cc saline delivered slowly, then 3 cc saline flush).

5.1.6 Route of Administration
The embolic mixture will be injected in small increments in the target geniculate artery(ies) after selective catheterization of the target vessel(s) using a microcatheter to reach distal arteries while avoiding branches that do not feed abnormal vessels.

5.1.7 Duration of Therapy
Treatment will be completed during one interventional session (visit 3, day 0).

5.2 Study Procedural Intervention(s) Description
On the day of the procedure (visit 3, day 0), the subjects will be given the choice of receiving intravenous anxiolytic and analgesic medication (moderate sedation) during procedure or proceeding with local anesthetic only. Arterial access site will be prepped and draped using sterile technique. Femoral artery access will be obtained with a micropuncture needle set and a vascular sheath or a guiding catheter will be placed in the femoral artery to maintain vascular access. A guiding catheter will be placed and lower extremity digital subtraction angiography (DSA) will be performed to depict the genicular arteries in all patients. Angiography will be performed to identify abnormal knee neovasculature arising from one or more of geniculate arterial branches.

After localizing the abnormal neovessels (abnormal vessels appear as tumor blush–type enhancement in the arterial phase, often accompanied by early venous drainage /hypervascular synovial tissue in the region of the target knee joint), a microcatheter will be inserted coaxially through the guiding catheter and selectively placed in the targeted artery(ies). If there is uncertainty about the angiographic findings, pre-embolization simulation can be performed with contrasted cone beam computed tomography (CBCT). This will allow the operators to know exactly what tissues will be receiving the microspheres. The abnormal vessels will be embolized with **100 µm Embozene™ Microspheres** solution under direct fluoroscopic visualization to prevent reflux and non-target embolization. Multiple geniculate arteries may be embolized until neovascularity is no longer seen.

The embolic mixture will be prepared by adding 9 cc of saline + 9 cc of contrast to the 2 cc Embosepheres for a total of 20 cc embolic mixture. Injection of the embolic mixture will continue in small increments until an end point of at least ‘pruning” of the hypervascular synovium in the target artery(ies) (0.5-1 cc embolic mixture injected over 2 minutes, followed by 1 cc saline delivered slowly, then 3 cc saline flush). In some cases, more selective catheterization will be performed by using the microcatheter to reach distal arteries while avoiding branches that do not feed abnormal vessels. After embolization, a repeat lower extremity angiogram and contrasted CBCT (if needed) will then be performed to evaluate for success of embolization and to exclude complication. The catheter(s) and sheath will be removed, and hemostasis of the arterial access will be achieved by an FDA-approved arterial closure device or manual compression and bed rest for 2-6 h after the femoral artery sheath removal. All participants will be monitored for 2-6 hours post procedure and any adverse events will be documented and managed. If hemostasis is obtained by a vascular closure device, it is anticipated that most participants will be discharged home 2 hours post procedure. If hemostasis is obtained by manual compression, it is anticipated that most participants will be discharged home within 2-6 hours post procedure.

Disposable syringes which spherical particulate will be discarded as medical waste and packaging will be kept in a secure location and/or packaging LOT number will be documented until the study is completed. Packages will be disposed of upon completion of the study.

5.2.1 Administration of Procedural Intervention
Procedures will be performed by an IRB-approved interventional radiologist with fellowship training in Vascular and Interventional Radiology. The interventional procedure will be performed during one session (day 0) with an approximate duration of the procedure estimated between 1-4 hours. Additional 2-6 hours will be needed after hemostasis of the access femoral artery is achieved for monitoring / observation. In general, the subject will be discharged home the same day (<23 hours) unless a complication arises that requires inpatient admission or overnight observation for management of the complication.

5.2.2 Procedures for Training of Clinicians on Procedural Intervention

All proceduralists performing the intervention will be vetted and credentialed by the site PI, with the following requirements for credentialing:

1- Fellowship trained in vascular and interventional radiology.
2- Board certified by the American Board of Radiology
3- License to practice medicine in New York
4- Performed at least three GAE procedures (cases performed during training are accepted) as a primary and/or assistant operator.

Prior to site activation, all investigators will complete a study training by the site PI and sign a training log.

6 Study Procedures and Schedule

6.1 Study Procedures/Evaluations

6.1.1 Study Specific Procedures

- Imaging assessment with knee MRA (visits 2, 6, and 8)
  - Baseline and follow-up (at 6 and 24 months) knee MRA will be performed.
- Biological specimen collection (visits 2, 5, 6, 7, and 8):
  - Baseline and follow-up biomarker analysis from blood, urine, and knee aspirate (synovial fluid) will be obtained from participants.
- Administration of questionnaires or other instruments for patient-reported outcomes (visits 2, 5, 6, 7, and 8):
  - VAS questionnaire
  - KOOS questionnaire
  - Self-reported quality of life EQ-5D-5L questionnaire
  - Anchor pain questionnaire
- GAE procedure (visit 3)
- Medical history (visits 2, 5, 6, 7, and 8):
  - Complete medical history will be obtained from medical records if available and/or by interview during clinic visits.
- History of previous and concomitant treatment (visits 2, 5, 6, 7, and 8):
  - Knee injections and frequency
  - Medication history. Will focus on medications currently taken for the treatment of knee pain; including prescription and over-the-counter medications for pain.
  - Physical therapy and frequency
  - Weight loss / gain
- Focused physical examination (visits 2, 5, 6, 7, and 8):
  - Vital signs (temperature, blood pressure, heart rate, oxygen saturation, height, weight, BMI)
  - Focused knee examination.

Note: A discussion of the results of any study specific procedures (e.g., radiographic or other imaging or laboratory evaluations) will be provided to participant after the completion of the study unless this information represents a significant health-related issue.

6.1.2 Standard of Care Study Procedures

- Standard of care imaging assessment with knee radiograph (visit 2):
  - Knee radiograph obtained within 3 months of the screening will be used to assess the knee.
  - A new knee radiograph will be obtained during or prior to visit 2 if no recent (within 3-month) radiograph of the target knee is available
  - Knee radiograph protocol: AP weightbearing, lateral, sunrise views
  - Knee radiographs will be assessed by a IRB-approved musculoskeletal radiologist

6.2 Laboratory Procedures/Evaluations

Baseline and follow-up biospecimen collection will be performed on visits (2, 5, 6, 7, and 8). Urine samples, peripheral venous blood draws, and knee aspirates (synovial fluid) will be obtained. Approximately 10 cc of blood will be collected from peripheral venous blood in each visit that requires collection of blood samples.

The samples will be sent to the NYU orthopedic lab for biomarker analysis.

- Storage location: These samples collected as part of the approved research protocol are stored and identified by barcodes and collection date only and kept in the NYU Langone Orthopedic Hospital.
- Access to samples: IRB-approved study team members from NYU Langone Orthopedic Hospital have access to these samples.
- Protecting subject anonymity: Study team members who have access to the samples will receive the biospecimen tubes labeled with study subject number and date of collection.
- Samples will be stored until the end of data analysis and study closure.

6.2.1 Other Assays or Procedures

Knee aspiration will be performed during baseline (visit 2) and follow-up visits (visits 5-8) when knee effusion is present to obtain synovial fluid for biomarker analysis. Baseline knee aspiration can be performed on the day of the procedure (visit 3) at the desertion of the investigator to minimize patient discomfort and pain as long as it's performed prior to the embolization. The procedure will be performed in the interventional radiology clinic, interventional radiology suite, or orthopedic clinic by an IRB-approved investigator after administration of local anesthetic. A needle will be advanced into the knee joint and approximately 10 cc of synovial fluid will be obtained and sent to the NYU orthopedic lab for biomarker analysis for later analysis (see section 6.2 for details of sample storage).

6.2.2 Specimen Preparation, Handling, and Storage

These samples (biospecimen) collected as part of the approved research protocol are stored and identified by barcodes and collection date only and kept in the NYU Langone Orthopedic Hospital. Processing and analysis will be performed by the biomarkers' lab.

6.2.3 Specimen Shipment

Specimen will be transferred to the biomarkers lab on the day samples are collected by an IRB-approved study coordinator in person.

6.3 Study Schedule

6.3.1 Screening (visit 1; Day -30 to -2)

In rheumatology, orthopedic, or vascular and interventional radiology clinic

- Obtain informed consent of potential subject
- Provide a copy of informed consent and key information sheet to subject
- Review subject's eligibility based on eligibility criteria
- Schedule study visits for eligible participants

Note: if subject prefers, visits 1 and 2 can be combined and procedures of these visits may be performed on the same day after completion of screening and obtaining informed consent.

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.

6.3.2 Enrollment/Baseline (visit 2, Day -30 to -1)

- Obtain medical history, concomitant medications, demographics information
- Targeted physical exam
- Administration of study questionnaires
- Previous / concomitant treatments
- Baseline MRA (if one is not available within the last 3 months)
- Baseline knee radiograph (if one is not available within the last 3 months)
- Biospecimen collection (including knee aspiration for synovial fluid collection)

6.3.3 Interventional visit (visit 3, Day 0)

- Performed within 30 days of visit 2
- Geniculate artery embolization (GAE) procedure
- Record any immediate complications / adverse events detected during the procedure or observation period (if applicable)
- Subjects will be given a phone number to reach a physician 24 hours a day to report any adverse symptoms and receive medical advice

6.3.4 Follow up Visits:

6.3.4.1 Follow up safety visit (Visit 4; day 7 ± 3 days)

- Subjects will be seen in clinic (in-person or telemedicine) or contacted by phone per subject's preference on day 7(± 3 days). As most complications of the procedure will be evident within this period, this visit is to evaluate for early AE's. If AE is suspected based on change in pain scores, functionality, or other signs / symptoms, further assessment and management will be performed based on the nature and severity of suspected AE.

6.3.4.2 Follow up visit at 3-month (Visit 5, Day 90 ± 10 days)

- Obtain medical history
- Record adverse events as reported by participant or observed by investigator (if applicable)
- Targeted physical exam
- Administration of study questionnaires
- Previous / concomitant treatments, including medical history
- Biospecimen collection (including knee aspiration for synovial fluid collection)

6.3.4.3 Follow up visit at 6 months (Visit 6, Day 180 ± 20 days)

- Obtain medical history
- Record adverse events as reported by participant or observed by investigator (if applicable)
- Targeted physical exam
- Administration of study questionnaires
- Previous / concomitant treatments, including medical history
- Biospecimen collection (including knee aspiration for synovial fluid collection)
- Follow-up knee MRA

6.3.4.4 Follow up visit at 12 months (Visit 7, Day 360 ± 30 days)

- Obtain medical history
- Record adverse events as reported by participant or observed by investigator (if applicable)
- Targeted physical exam
- Administration of study questionnaires
- Previous / concomitant treatments, including medical history
- Biospecimen collection (including knee aspiration for synovial fluid collection)

6.3.4.5 Follow up visit at 24 months (Visit 7, Day 720 ± 40 days)

- Obtain medical history
- Record adverse events as reported by participant or observed by investigator (if applicable)
- Targeted physical exam
- Administration of study questionnaires
- Previous / concomitant treatments, including medical history
- Biospecimen collection (including knee aspiration for synovial fluid collection)
- Follow-up knee MRA

6.3.5 Withdrawal/Early Termination Visit

- Obtain medical history
- Record adverse events as reported by participant or observed by investigator (if applicable)

- Targeted physical exam
- Administration of study questionnaires
- Previous / concomitant treatments, including medical history
- Biospecimen collection (including knee aspiration for synovial fluid collection)

6.3.6 Unscheduled Visit
Unscheduled visits if needed will be documented in the medical chart of the subject including the reason for the visit and assessment / management plan as determined by the visit.

6.4 Concomitant Medications, Treatments, and Procedures
All relevant concomitant medications taken during study participation, as well as treatments and procedures will be recorded. Medications to be reported are concomitant prescription medications, over-the-counter medications and non-prescription medications used pain management. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

6.5 Justification for Sensitive Procedures
Not applicable.

6.5.1 Precautionary Medications, Treatments, and Procedures
Not applicable.

6.6 Prohibited Medications, Treatments, and Procedures
Not applicable.

6.7 Prophylactic Medications, Treatments, and Procedures
Not applicable.

6.8 Rescue Medications, Treatments, and Procedures
In the event of non-target embolization during the procedural visit leading to limb ischemia, subsequent interventions and / or medical management may be required for treatment of limb ischemia as medically indicated based on standard medical practice for treatment of limb ischemia.

6.9 Participant Access to Study Agent at Study Closure
After participants are no longer enrolled in the study, they will return to standard of care treatment for knee pain.

7 Assessment of Safety
7.1 Specification of Safety Parameters
Safety parameters include the number, severity, causality, timing, and description of complications, adverse events, or poor outcomes that are secondary to the procedure.

7.1.1 Definition of Adverse Events (AE)
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures or studies on target knee in the follow-up period after the study intervention are also considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Definition of Serious Adverse Events (SAE)
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

A ***serious adverse event*** is any AE that is:

- fatal
- life- or limb- threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life or limb threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.1.3 Definition of Unanticipated Problems (UP)

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 application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an 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 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 (21 CFR 812.3(s)).

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, severe, life-threatening / disabling event, or death / unexpected pregnancy abortion. The investigator will also categorize each adverse event as to its potential relationship to study device.

The severity and causality of all adverse events will be graded according to the new adverse event classification by the Society of Interventional Radiology Standards of Practice Committee [62], as follows:

- **Mild AE:** No therapy or nominal (non-substantial) therapy (postprocedural imaging performed and fails to show manifestation of AE); near miss (e.g., wrong site of patient prepared, recognized and corrected before procedure, wrong patient information entered for procedure);
- **Moderate AE:** moderate escalation of care, requiring substantial treatment, e.g., intervention (description of intervention and result of intervention) under conscious sedation, blood product administration, extremely prolonged outpatient observation, or overnight admission after outpatient procedure not typical for the procedure (excludes admission or hospital days unrelated to AE);
- **Severe AE:** marked escalation of care, i.e., hospital admission or prolongation of existing hospital admission for > 24 hours, hospital admission that is atypical for the procedure, inpatient transfer from regular floor/telemetry to intensive care unit, or complex intervention performed requiring general anesthesia in previously non-intubated patient (generally excludes pediatrics or in circumstances in which

general anesthesia would primarily be used in lieu of conscious sedation, e.g., in mentally challenged or severely uncooperative patients);
- **Life-threatening or disabling event:** e.g., cardiopulmonary arrest, shock, organ failure, unanticipated dialysis, paralysis, loss of limb or organ;
- **Patient death or unexpected pregnancy abortion**.

7.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below according to the new adverse event classification by the Society of Interventional Radiology Standards of Practice Committee

- Category 1: AE not caused by procedure. The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.
- Category 2: Unknown whether AE was caused by the procedure.
- Category 3: AE caused by the procedure. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

The definition implies a reasonable possibility of a causal relationship between the event and the study device. This means that there are facts (evidence) or arguments to suggest a causal relationship**.**

The following factors should also be considered:

- The temporal sequence from study procedure: The event should occur after the study procedure. The length of time from study procedure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant procedures / treatments: The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study procedure: Clinical and/or nonclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

7.2.3 Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study device.

7.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by one of investigators. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedure (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

7.4 Reporting Procedures – Notifying the IRB

7.4.1 Adverse Event Reporting

The principal investigator will promptly notify the IRB of any unanticipated problems (UP) involving risks to subjects or others that occurs during the course of a study within **five working days** of learning about the event using Research Navigator.

7.4.2 Serious Adverse Event Reporting

Serious adverse events will be captured from the time of the main study's informed consent through 30 days after the last follow-up visit. The principal investigator will promptly notify the IRB of any unanticipated problems involving risks to subjects or others that occurs during the course of a study within **five working days** of learning about the event using Research Navigator.

According to 21 CFR 812.150(a)(1), the investigator will submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. In addition, according to 21 CFR 812.150(b)(1), the sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) will report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor will submit such additional reports concerning the effect as FDA requests.

7.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- **UPs that are SAEs** will be reported to the IRB within **5 working days** of the investigator becoming aware of the event.
- **Any other UP** will be reported to the IRB within **10 working days** of the investigator becoming aware of the problem.

7.4.4 Reporting of Pregnancy

If the subject participating in the study is found to be pregnant during the study period, participant will immediately be withdrawn from the study and IRB will be informed.

7.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor (PI) within 24 hours of awareness.
- Other SAEs regardless of relationship will be submitted to the study sponsor (PI) within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

7.6 Reporting Procedures – Notifying the FDA

The study sponsor (PI) is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/IDE safety reports.

The following describes the IDE safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 10 working days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study device, and
  - unanticipated,
    regardless of the seriousness of the event.

- ***Within 5 working days*** *(via written report)*
  - Protocol deviation to protect the life of the subject in emergency
  - Withdrawal of IRB approval
  - Lack of informed consent

Reporting Process

Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form [available in study regulatory binders], or in a narrative format.

7.7 Study Halting Rules
Administration of study device will be halted when three severe AEs determined to be “probably related” or “related” to the study device are reported to the study sponsor. In such cases, enrollment screens will stop accepting new study participants until determination of safety is reviewed by the study sponsor. The study sponsor will inform the FDA of the temporary halt and the disposition of the study.

7.8 Safety Oversight
It is the responsibility of the sponsor/Principal Investigator (PI) to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan.

Medical monitoring will include a regular assessment of the number and type of serious adverse events. Data (demographics, eligibility criteria), screening methods, and adverse events also will be assessed by the PI who is a fellowship trained interventional radiologist and licensed physician monthly to ensure study safety, compliance, and integrity/accuracy of data in accordance with the data safety monitoring plan.

An sub-investigator with orthopedic surgery specialty will be consulted for safety and adverse event evaluation prior to final determination by the study PI.

Administration of study procedure will be halted when three severe AEs determined to be “probably related” or “related” to study device are reported to the sponsor (PI). The PI will notify the study investigators immediately when the third grade 3 event is reported, and enrollment screens will stop accepting new study participants. The study sponsor will convene a meeting with study investigators by teleconference or in writing as soon as possible and will provide recommendations for proceeding with the study. The study sponsor will inform the IRB and FDA of the temporary halt and the disposition of the study.

The outcomes of these reviews, when adverse events are captured will be communicated directly with the IRB. A summary of these reviews will be submitted to the IRB as part of an annual progress report at Continuing Review.

8 Clinical Monitoring
Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the study PI once every 3 months.

Monitoring activities include communication with the sub-investigators and study site staff; review of the study site’s processes, procedures, and records; and verification of the accuracy of data.

9 Statistical Considerations
9.1 Statistical and Analytical Plans (SAP)
A formal SAP will not be performed prior to database lock since this study is a pilot study with no randomization.

9.2 Statistical Hypotheses
This is a single arm study (i.e., no sham, placebo or alternative treatment included). The primary objective (clinical success rate) is a binary assessment of whether or not each patient achieved clinical success at 6 months post intervention.

The study is designed to test the null hypothesis (H0) that the true proportion (PT) of patients that will manifest a positive treatment response, is no greater than 0.5 against the one-sided alternative hypothesis (HA) that PT ≥ 0.75.

The response rate will be summarized in terms of the observed proportion of patients manifesting a positive response and a two-sided exact 95% confidence interval (CI) per the Blyth-Still-Casella method (31). The treatment will be declared a success if the data support the conclusion that at least 75% of treated patients can be expected to show a positive response. The treatment will be considered unworthy of additional study without further

development if the data are consistent with the conclusion that no more than 50% of treated patients can be expected to show a positive response.

9.3 Analysis Datasets

Participants who received study device and complete at least one follow-up visit (3-month visit) will be included in the study analysis.

Preliminary analysis will be performed after 25% (10 subjects) of study sample size complete the 6-month follow-up visit.

9.4 Description of Statistical Methods

9.4.1 General Approach

This is a single arm study (i.e., no sham, placebo or alternative treatment included). The primary objective (clinical success rate) will be assessed as a binary outcome of whether or not each patient shows clinical success as defined above. The response rate will be summarized in terms of the observed proportion of patients manifesting a positive response and a two-sided exact 95% confidence interval (CI) per the Blyth-Still-Casella method. KOOS pain scores and pain VAS will be assessed as mean and standard deviation.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint is the clinical success rate at 6-month follow-up compared to baseline as a binary assessment.

9.4.3 Analysis of the Secondary Endpoint(s)

Analysis of secondary endpoints include: (1) changes in the mean KOOS and VAS pain scores, the mean (2) the technical success rate (defined as the proportion of patients for whom the procedure was successfully completed); (3) the adverse event rate (defined as the proportion of patients showing each type of adverse event or any adverse event); (4) reduction in the usage of pain medication and the need for physical therapy. A point estimate and 95% confidence interval will be provided for each secondary outcome at each time and for the change in each outcome from baseline to each post-treatment follow-up visit. Changes in the outcomes from baseline to follow-up will be tested using the paired-sample Wilcoxon signed rank test for the KOOS and VAS scores and the McNemar test for the other measures which will be assessed as binary outcomes (e.g., whether or not the patient reported usage of pain medication on a daily basis).

9.4.4 Safety Analyses

Safety endpoints will assess adverse event rate (defined as the proportion of patients showing each type of adverse event or any adverse event). The severity and causality of all adverse events will be graded according to the new adverse event classification by the Society of Interventional Radiology Standards of Practice Committee.

9.4.5 Planned Interim Analysis

Preliminary analysis will be performed after 25% (10 subjects) of study sample size complete the 6-month follow-up visit.

9.5 Sample Size

The sample size is selected based on primary objective so that the study will have 80% power at the 5% significance level for testing the null hypothesis H0: PT ≤ 0.5 against the alternative hypothesis HA: PT ≥ 0.75, where PT is the true proportion of patients that will manifest a positive treatment response. As a result, the study should have 40 patients who completed the 6 months visit since this sample size will endow the test with 80.4% power at a realized significance level of 0.047 with 20% attrition, the study will need 50 subjects to reach the target sample size.

With 20% with 20% attrition, the study will need to enroll 50 patients. The PI and sub-investigators determined that increase in the sample size is necessary to evaluate the role of GAE as a disease-modifying treatment option for knee OA. Since this current study is the only active study in the U.S collecting samples for biomarker analysis and the need for a larger sample size to evaluate changes in biomarker levels, an increase in sample size is needed.

10 Source Documents and Access to Source Data/Documents

Source data is 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 or other imaging stdudies, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use paper CRFs as source documents. Source CRFs can also be documented in the electronic medical record (EPIC).

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 ink if paper CRFs used. 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. ERRORS WILL NOT BE ERASED OR WHITED OUT. For clarification of illegible or uncertain entries, clarification will be printed above the item, then initialed and dated.
Access to study records will be limited to IRB-approved members and the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups 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.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups 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.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution.

The PI will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

All investigators will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

12.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The consent form is submitted with this protocol.

12.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

12.4 Vulnerable Populations

12.4.1 Adults without Capacity to Consent

Subjects without capacity to consent will not be enrolled in this study. No surrogate consent will be allowed.

Since this research does not involve recruitment of individuals with impaired consent capacity, judgment that prospective subjects have the capacity to consent to the research can ordinarily be made during routine interactions with the individual during the consent process. An investigator who questions a prospective subject's capacity to consent will enroll the individual and should consult with the IRB.

12.4.2 Surrogate Consent

Surrogate consent will not be allowed in this study.

12.5 Posting of Clinical Trial Consent Form

This study does not meet the requirements for posting of clinical trial consent form since it's not funded by a federal agency.

12.6 Participant and Data 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). Those regulations require a signed subject authorization informing the 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.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Health. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by NYU Langone Health research staff will be the Institution-approved, encrypted and HIPAA-compliant version of TrialMaster managed by MCIT if an electronic data collection tool or data base is used. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Health.

12.6.1 Research Use of Stored Human Samples, Specimens, or Data

Intended Use: data collected under this protocol may be used to study the effect of GAE in treatment of patients with persistent knee pain after TKA. No genetic testing will be performed.

Storage: Access to stored samples will be limited to study personnel. Samples will be destroyed after the termination or completion of the study. Data will be stored only on TrailMaster and electronic medical records (EPIC) as well as any paper source documents (in subject study files). Electronic data will be kept in password-protected computers. Paper forms will be stored in the research office, that has a door lock, and locked cabinets. Locked cabinets access will only be provided to study PI and coordinator. Only investigators will have access to the data.

12.7 Future Use of Stored Specimens

Biospecimens collected for the study will be stored for use only in this study. Specimens will not be stored for future research beyond the scope of the study.

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Trial Master internal, a 21 CFR Part 11-compliant data capture system provided by NYU Langone. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

13.4 Publication and Data Sharing Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.

- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

14 Study Finances

14.1 Funding Source

Department of Radiology.

The device manufacturer will not be providing the device for free, is not funding this trial in any capacity, and the data / specimens collected from this study will not be shared directly with the manufacturer beyond publicly available publications in peer-reviewed journals.

14.2 Participant Reimbursements or Payments

No reimbursement or payments will be offered to participate in this study.

15 Study Administration

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the PI and a study co-investigator.

16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

17 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments:

1- Attachment 1_Embozene Derections for use (DFU)
2- Attachment 2_IDE G230245_Approval Letter
3- Attachment 3_Study Brochure
4- Attachment 4_Recruitment_Written Notification
5- Attachment 5_Recruitment_Tepehone Script
6- Attachment 6_Study Questionnaire

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19 Schedule of Events

X	Visit 1*	Visit 2*	Visit 3	Visit 4**	Visit 5#	Visit 6#	Visit 7#	Visit 8#
Visit Description	**Screening Day -30/-2**	**Baseline Day -30/-1**	**Intervention Day 0**	**7-day safety visit ± 3 days**	**3-month follow-up ± 10 days**	**6-month follow-up ± 20 days**	**12-month follow-up ± 30 days**	**24-month follow-up ± 40 days**
Eligibility screen	X							
Informed consent	X							
Demographics		X						
Medical history		X			X	X	X	X
Physical exam		X		X (if in person)	X	X	X	X
Pain VAS		X			X	X	X	X
KOOS Questionnaire		X			X	X	X	X
EQ-5D-5L scale		X			X	X	X	X
Previous treatments		X			X	X	X	X
Venous blood draws		X#			X	X	X	X
Urine samples		X#			X	X	X	X
Synovial fluid		X#			X	X	X	X
Anchor questionnaire					X	X	X	X
Knee MRA		X[1]				X[3]		X[3]
Adverse Events			X	X	X	X	X	X
Knee radiograph		X[2]						
GAE			X					

1- If not previously available (i.e., recent knee MRA **within 3 months** of screening); if MRA cannot be obtained on the same day due to subject preference and/or MRI scheduling related reasons, MRA can be performed anytime between the baseline visit and intervention visit.
2- If not previously available (i.e., recent knee radiograph **within 3 months** of screening). Can be performed on a separate day based on appointment availability or subject's preference.
3- Post-intervention MRAs can be done on a separate day (visit 6 and visit 8) based on appointment and subject's availability as long as it's performed within the timeframe of the visit.

***** Visit 1 and 2 can be combined and performed on the same day.
** Visit 4 (7-day safety visit) can be performed over the phone, telemedicine, or in-person clinic visit determined by subject's preference and need for physical examination.

Baseline samples for biomarker analysis (blood, urine, and synovial fluid) can be done on the day of the procedure prior to initiation of procedure (GAE).